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Editorial

BAL (British Anti-Lewisite)

THE history of specific antidotes to poisoning by metals is substantially an account of unfulfilled promises. The long succession of failures was interrupted, however, in the early days of World War II by a series of important discoveries made in rapid succession in the cooperative war programs of chemical, pharmacologic and clinical research focused on the problem of an antidote to the arsenical vesicant, Lewisite. The chief practical issue was the synthesis of the compound BAL which is not only highly effective in preventing tissue damage by arsenic and mercury but also in reversing moderate grades of tissue injury after the metals have been at work for some time.

The numerous lines of investigation leading to this discovery were recently reviewed by Peters, Stocken and Thompson of Great Britain, and by Waters and Stock of this country. Many important steps were necessary before the problem arrived at the point at which an effective antidote became available. One of the earliest observations bearing most directly on the subject was that of Voegtlin, Dyer and Leonard of the United States Public Health Service who, in 1923, advanced the view that the therapeutic arsenicals produce their effects by combining with the —SH groups of protoplasm. There were observations that various enzyme systems depended on the free —SH group for their activity, that these enzyme systems could be poisoned by arsenicals, that the combination in some types of

thioarsenites could be reversed in alkaline solution, that monothiol and some dithiol compounds with arsenic were as toxic as the arsenical itself; observations leading to the belief that fairly stable but reversible ring compounds might be formed between the arsenical and the —SH groups of tissue proteins or the protein portion of the enzyme systems and that similar but less easily dissociable compounds of the arsenicals are formed by their interaction with simple dithiols which can compete successfully with the tissue dithiols for the toxic metal.

The compound 2,3-dimercaptopropanol, more popularly known as British anti-Lewisite or BAL, is not a harmless material. It is itself a poison. It is an irritant to the skin and mucous membranes and in large doses causes death with capillary paralysis and shock, sometimes preceded by convulsions. It causes lacrimation, blepharospasm, salivation, vomiting, muscular cramps, unrest, apprehension and weakness. Small doses produce arteriolar constriction with elevation of the blood pressure. It is noteworthy that unpleasant effects are produced by doses much below those which may cause serious damage, a fact which provides an element of safety against overdosage. BAL is rapidly eliminated in animals and man and doses may be repeated in man at intervals of three or four hours without significant cumulation. Studies in man show that some of the minor toxic effects may be produced by doses as small

as 3 to 5 mg. per Kg. although single doses as high as 8 mg. per Kg. have been given with safety by intramuscular injection. BAL may be used by most of the common routes of administration, subcutaneous, intramuscular and intravenous injection, dilute applications to the eye and by skin incunctions. It is best given by intramuscular injection in the form of a 10 per cent solution in peanut oil.

In human poisoning with arsenical compounds, the administration of BAL gives rise to a prompt and marked increase in the arsenic content of the blood which is associated with a marked increase in the arsenic excretion in the urine. There now exist convincing reports on the value of BAL as an antidote against dermatitis, encephalitis, agranulocytosis and the various febrile reactions due to the arsenicals. There is some doubt concerning its utility in arsenical jaundice. The best results are obtained when the antidote is given fairly promptly after the poison has been taken but it proves effective even after considerable injury has been produced by the arsenical.

The problem has been carried to the field of other metals and evidence has been obtained in the laboratory that such heavy metals as lead, antimony, vanadium, bismuth, cadmium, mercury and zinc inactivate —SH-containing enzymes and that these effects can be reversed by members of the BAL series.

Considerable advance has been made in the application of BAL as an antidote to bichloride of mercury poisoning. The results of experiments in rabbits and dogs by Gilman and his collaborators showed a high degree of protection against the systemic effects of mercury even when treatment was delayed for two or three hours, indicating that the dithiols may remove mercury from its combination with the cell proteins. BAL has been applied successfully by Longcope and his collaborators in the treatment of patients with bichloride of mercury poisoning. Again, while the best results are obtained when the antidote is administered soon, dramatic relief of symptoms

and complete recoveries occurred in patients treated with BAL under conditions which rarely allowed for recovery with any previous forms of treatment. In a fairly large series of cases of poisoning at the Johns Hopkins Hospital in which the patients swallowed 1 Gm. of bichloride of mercury or more, and admission was delayed for periods up to four hours, all those treated with BAL recovered while the mortality rate in similar controls was about 30 per cent. BAL has also been shown to be effective against the toxic effects of the organic mercurial salyrgan in the mouse, the cat and the dog. This is of considerable importance in view of the extensive use of these diuretics and the possibility of accidental overdosage.

There seems to be very little doubt of the efficacy of BAL as an antidote to arsenic and mercury poisoning. Isolated observations have already been made on the effect of BAL in human poisoning by other metals, copper, zinc and gold. Several rather striking results have been reported on the use of BAL in poisoning produced by gold employed in the treatment of arthritis.

Much remains to be learned about the possibilities of thiols in the treatment of poisoning by various metals. It may well be that other mercaptans may prove safer and more effective than BAL itself. Since it is likely that clinicians will be turning to BAL as a form of treatment of human poisoning by many metals, the experience with cadmium should be borne in mind. It was shown in animals that while the prophylactic administration of BAL eliminated the signs of acute intoxication with cadmium chloride, the animals later succumbed to renal damage in the process of excretion of the cadmium-BAL complex. It is clear from this that great caution is necessary in the application of BAL to poisoning by metals in man and that thorough exploration of the problem relating to any particular metal should be made in animals before BAL is applied in cases of human poisoning.

HARRY GOLD, M.D.

Effects of Immobilization upon Various Metabolic and Physiologic Functions of Normal Men^{*}

JOHN E. DEITRICK, M.D., G. DONALD WHEDON, M.D.

and

EPHRAIM SHORR, M.D.

with the technical assistance of

VINCENT TOSCANI *and* VIOLA BUNIAK DAVIS

New York, New York

THERE has been a growing concern in recent years not only over the possible relation of bed rest to a variety of hazardous complications commonly encountered during illness but also as to its optimal use as a therapeutic measure during convalescence. During World War II interest in these problems was heightened by the importance to the armed forces of methods whereby the convalescence and rehabilitation of disabled soldiers might be accelerated. This has led to the initiation of studies designed to clarify the physiologic and metabolic derangements associated with traumatic and infectious states as well as the manner in which they are influenced by bed rest.

The value of the information provided by any such study will depend upon the appreciation of the many factors participating in the reaction of the organism to stress and upon the extent to which differentiation of these factors has been made possible by the conditions under which the observations have been carried out. The complexity of the factors involved is apparent from a consideration of the variety of phenomena

which have been attributed to bed rest. These range from the relatively acute pathologic complications such as phlebotrombosis, pulmonary embolism and hypostatic pneumonia to the more chronic pathologic and functional disturbances which include decubitus ulcers, nephrolithiasis, constipation, myasthenia and many metabolic and vascular functional derangements. Their variety suggests a multiple origin, indicating that investigation of any of these phenomena would require exacting analysis of numerous underlying mechanisms. In any investigation of the rôle of bed rest in disease and convalescence, there are many varying conditions which may exert an influence. It is necessary to consider observations in relation to the amount of activity permitted to the patient. In most discussions, bed rest has been a poorly defined term, activity in bed being inadequately described or controlled. It may vary from the complete inactivity of the comatose patient or one with a fractured spine to the constant movement of the patient with Graves' disease. Some attention should also be directed to the phase of the illness and

^{*} From The Department of Medicine, Cornell University Medical College, The New York Hospital and The Russell Sage Institute of Pathology. This investigation was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

duration of bed rest. A differentiation must be made of the effects of other therapeutic agents from the effects of bed rest. Finally, it is necessary to differentiate the derangements which are presented by a patient bedridden by illness from those which might be attributed to bed rest *per se*, that is, from those derangements which would be experienced by a normal healthy person subjected to the same conditions.

There are few published experiments which satisfy these criteria, a circumstance which is largely responsible for the present controversial status of bed rest as a therapeutic measure. This uncertainty, and also the sparsity of factual or quantitative data, is reflected in the numerous recent criticisms of bed rest¹⁻⁴ which have led to the present vogue of early postoperative ambulation.⁵⁻⁹ A review of the available literature disclosed only two experiments which have attempted to differentiate under controlled conditions between the effects of bed rest or immobilization *per se* and the effects of disease. In 1929, Cuthbertson¹⁰ studied a group of normal subjects maintained on constant diets during periods of bed rest of ten to fourteen days. The bed rest was standardized by the use of splints and sandbags. The brevity of both the control periods and the periods of immobilization reduced the value of these experiments. In 1944, Keys¹¹⁻¹³ carried out similar studies in young normal individuals. They were not restrained by splints or casts and, except for short periods, their activity in bed was unrestricted. In addition, their dietary intake was reduced during the periods of bed rest.

The purpose of the present investigation was to obtain quantitative metabolic and physiologic data on the effects of immobilization on normal, healthy individuals and thus to furnish a basis for differentiating the effects of immobilization *per se* from those which might arise from (or be superimposed by) disease or trauma. The experiment was devised in such a manner as to define and keep constant the activity in bed and to exclude or to control carefully other

factors such as disease, diet and environment throughout the period of observation.

PROCEDURE

Four normal, healthy men were studied on constant diets before, during, and following a prolonged period of bed rest. Activity in bed was standardized by immobilization of the pelvic girdle and legs in plaster casts. This was done to avoid the variable amount of activity that young healthy subjects lying in bed might exhibit. The study was carried out on the metabolism ward of the New York Hospital and the Russell Sage Institute of Pathology.

The investigation was planned to include metabolic balance studies in nitrogen, calcium and phosphorus and the analysis of the urine for creatine, creatinine, citric acid and 17-ketosteroids. The investigation was further planned to make observations and tests of circulatory, respiratory, muscular and other physiologic functions. Since a complete study of the effects upon each function was impossible, certain tests in each field were selected which might be expected to yield the most pertinent information and indicate the direction which later studies might follow.

The length of the control period was six to eight weeks, the immobilization period six weeks in the first pair of subjects and seven weeks in the second pair. The recovery period in the first pair was four weeks; this was found to be too short and was lengthened to six weeks in the second pair.

During the control period the subjects were active; in addition to being up and about on the metabolism ward, they took exercise in the form of calisthenics one-half hour and swimming one-half hour each day and were taken by an escort on one-hour walks outside the hospital three or four times a week.

During the immobilization period the subjects were placed in bi-valved plaster casts extending from the umbilicus to the toes. They remained in these casts constantly throughout the immobilization period except for the use of the bed pan and for the ergometer and tilt table tests. Time free of the cast averaged thirty to forty minutes daily. (The plaster cast was first applied to a subject during the early "adjustment" phase of the control period and when dry (thirty-six hours) was bi-valved and removed, the subject returning promptly to control activity. The cast was then padded and fitted with ties in prepara-

tion for occupancy during the immobilization phase.)

In the recovery period, the subjects were ambulant on the sixth day and two weeks after coming out of the casts resumed the same level of activity as they pursued in the control period.

The protein intake was set at slightly less than 1.5 Gm. per Kg. body weight and was more than adequate to maintain nitrogen equilibrium during the control periods. Calcium, phosphorus and potassium were kept constant at medium levels. Sodium intake was not kept constant in

TABLE I
DAILY DIETARY INTAKE AND PHYSICAL CHARACTERISTICS OF SUBJECTS

Subject	Age	Height, Cm.	Weight, Kg.	Calories, Daily Intake	Protein, Gm.	Fat, Gm.	CHO, Gm.	Ca, Gm.	P, Gm.	Na, Gm.	K, Gm.
E. M.	29	177	66	2,500	85	110	292	0.852	1.50	3.15
C. O.	20	179.5	62	2,800	90	114	352	0.920	1.64	3.76
A. S.	25	161	60	2,800	90	114	352	0.920	1.64	4.00	3.76
S. W.	20	181	64	2,800	90	114	352	0.920	1.64	4.00	3.76

The first pair of subjects was studied from August to December, 1944, and the second pair from February to June, 1945.

Subjects. Conscientious objectors volunteered as subjects for this experiment and were transferred to the hospital by Selective Service. They were healthy young men, varying in age from twenty to twenty-nine years. Physical characteristics of age, height and weight are listed in Table I.

The subjects differed considerably in body type. E. M. was of medium height and moderately muscular. A. S. was a Nisei, rather short and of excellent muscular development. C. O. and S. W. were rather tall and slender. The only physical defect in the group was found in S. W. who had an accentuated first heart sound at the mitral area, pulmonic second sound louder than aortic second sound and on exercise a short, rolling, crescendo, presystolic murmur at the mitral area. However, his heart was not enlarged, the left auricle did not compress the esophagus, the electrocardiogram was normal and the heart showed excellent reserve power.

Diets. The diets (Table I) were selected at such levels that they could be kept constant throughout all periods of the experiment. They were calculated to maintain the subjects in caloric, mineral and nitrogen balance during the control periods, yet permit complete ingestion during immobilization. One subject (E. M.) received 2,500 calories; the other three, 2,800 calories. The diets were not creatine-creatinine free and for each of the diets there were actually three daily menus which were rotated in succession.

the first pair of subjects but was in the second pair.

Calculated values for the caloric and mineral content of the various foods were obtained largely from the sixth edition of Sherman.¹⁴ Values for grapejuice were obtained from the fourth edition of Sherman, for rye bread from Rose¹⁵ and for cereals from McCance and Widdowson.¹⁶

A total of twelve diet analyses (*in toto* method) was carried out during the course of the studies. The average percentage of the calculated values recovered by analysis was 96.5 per cent for nitrogen, 98.2 per cent for calcium and 93.1 per cent for phosphorus. In the balance studies of these three elements the calculated values were taken as the intake. For potassium, 83.7 per cent of the calculated values was recovered on analysis of the diets and for sodium 108.3 per cent was recovered on analysis as compared with the calculated values. Since the tables used to obtain the sodium and potassium content of foods were incomplete and of questionable validity, the values we obtained by analysis were used as the intake for the balance studies of these two elements. (When tables later became available giving the sodium and potassium content of foods based on analyses made by the flame photometer,¹⁷ recalculation of the contents of the diets when compared with the diet analyses revealed that the average percentage of the calculated values recovered on analysis was 89.3 per cent for potassium and 99.8 per cent for sodium.) In the second pair of subjects (A. S. and S. W.), the sodium intake was kept constant at 4.0 Gm. per day by giving measured

amounts of sodium chloride to be sprinkled over the food.

Methods. A. Chemical studies: A general description of the ward routine and methods employed on the metabolism ward of the Russell Sage Institute of Pathology and the New York Hospital has been given by E. F. DuBois.^{18,19}

The measured diets and collection of specimens for the chemical balance studies were begun the day after the subjects' arrival on the ward. It was found that it took from one week to ten days for adjustment to the diet and ward routine as judged by the establishment of relative stability in the day to day output of chemical constituents.

The metabolic balance studies were carried out in seven-day periods. Fecal nitrogen, calcium, phosphorus, sodium and potassium were determined by chemical analysis. Urinary calcium, phosphorus and citric acid were determined daily in the first two subjects studied and on four- and three-day pooled specimens in the subsequent studies. Urinary sodium, potassium, inorganic sulfur and 17-ketosteroids were determined on seven-day pooled specimens.

Urine specimens were preserved by refrigeration and the addition of 20 cc. of toluol to each twenty-four-hour collection. To the seven-day pooled specimens, made up of aliquots of the twenty-four-hour collections, was added 10 cc. of concentrated HCl.

Stool specimens were collected in individual covered enameled containers which were kept in the ice box. The stool periods were marked by giving by mouth 0.2 Gm. carmine at 9 P.M. on the last day of the period. Stool specimens were evaporated to dryness, weighed, ground and completely mixed. (Drying of a stool was begun within one day of the time it was passed in order to prevent decomposition.)

Diets were analyzed *in toto*, one day's entire menu being mixed together, ground and then prepared for analysis in the same manner as in the preparation of a stool for analysis. Blood was drawn for analysis when the subjects were in the fasting, basal state. Specimens were allowed to stand at room temperature for two hours, then centrifuged twice and the serum withdrawn.

Urine and stool specimens were analyzed for nitrogen by a modification of the Kjeldahl method;²⁰ for stool nitrogen analysis an aliquot of the dry stool was placed directly in a Kjeldahl flask. Urine and stool specimens were analyzed for phosphorus by the method of Fiske and Sub-

barow.²¹ Calcium in the urine was determined by the method of Shohl and Pedley;²² the preparation of stool for calcium analysis was carried out as outlined in Hawk and Bergcim²³ and the neutralization and analysis by the method of Shohl and Pedley.²² The creatine content of the urine was determined by the method of Benedict;²⁴ creatinine by the method of Folin;²⁵ citric acid by the method of Taussky and Shorr²⁶ and total sulfate (inorganic and etheral) sulfur by the method of Folin.²⁷ Urine pH was determined in a Hydrogen Ion Concentration Meter. The excretion of 17-ketosteroids in the urine was determined by a modification²⁸ of the method of Callow, Callow and Emmens;²⁹ the ketosteroids were hydrolyzed and extracted (three times) by shaking with carbon tetrachloride at room temperature; the extract was cleared of estrogens with sodium hydroxide and water and the final extract prepared according to the original method. Sodium and potassium in serum, urine and stool were determined by a flame photometer, designed by Barnes, Richardson, Barry and Hood³⁰ and the analyses carried out by the methods of Hald³¹ and Toscani and Buniak.³² The sodium and potassium analyses of the blood were determined on diluted samples of serum and analyses of urine on diluted urine specimens; the analyses of food and stool were carried out upon weakly acidified solutions of ash prepared in the same manner as for calcium analysis.²³ Serum specimens were analyzed for calcium by the method of Clark and Collip,³³ phosphorus by the method of Fiske and Subbarow²¹ and total proteins by the Kjeldahl method.²⁰ Blood prothrombin levels were determined by a modification of the method of Herbert.³⁴

Creatine tolerance tests^{35,36} were performed in the following manner: Since the diets were not creatine-free, the subjects were given the same menu for three successive days. On the second of the three days, the subjects were given 1.32 Gm. of creatine hydrate at 10 A.M. The test dose of creatine hydrate, 1.32 Gm., is equivalent to 1.0 Gm. of creatine in the urine expressed as creatinine. The control creatine excretion was taken as the average of the first day's excretion and the excretion of the two days in the preceding week upon which the subject received the same menu as during the test days. Calculation of the percentage of fed creatine retained, i.e., the creatine tolerance, was based on the total excretion of the day of and the day follow-

ing the administration of the test dose of creatine. From the excretion of each of these two days the control excretion was subtracted. The difference represented that fraction of the ingested creatine which was not retained. This figure, when divided by the total amount of creatine which might have been excreted (1.0 Gm.) from the test dose, represented the per cent excreted. Subtracting this figure from 100 per cent yielded as a result the percentage of fed creatine retained. The minimum normal value for creatine tolerance is 70 per cent.

Biologic assay of adrenal corticosteroids in the urine by the determination of the amount of glycogen deposited in the liver of adrenalectomized mice³⁷ was carried out for us by Dr. Konrad Dobriner of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York. The determinations were made on two subjects, E. M. and C. O., on seven-day pooled specimens during the last four control weeks and during the immobilization and recovery periods.

B. Physiological studies: Subjects were weighed daily during the control and recovery periods. During immobilization they were weighed twice weekly in the casts on a weighing table, the weight of the cast and the table being subtracted. The basal metabolic rate was determined weekly by the method of Benedict and Roth.³⁸

Muscle power was measured every four to eight days during the control periods and every ten days during the immobilization and recovery periods on an ergometer, a modification of the ergograph designed by Co Tui.³⁹ The ergometer differs from the Co Tui ergograph in being fitted with a Kirsten adjustable Thomas splint and a Chatillon spring scale against which the subject pulled. The ergometer was designed to test muscle groups in all four extremities with the subject supine: (a) the biceps group in the flexed arm pull (elbow at 90 degrees); (b) the shoulder and arm muscles in the straight arm pull; (c) the anterior tibial group in the foot pull (leg straight) and (d) the gastrocnemius-soleus group in the foot push. Muscle power was taken as the number of pounds pull (best one of three) from the spring scale; there was a two-minute rest between each pull in order to avoid fatigue. Strength of grip was measured on a hand dynamometer. Studies of the rate of muscular fatigue were attempted in several ways but it was found that motivation played too great a rôle and the studies were therefore discontinued. (For the

ergometer tests during the immobilization period (every ten days) the subject slept out of the cast the night preceding the test to lessen muscle and joint stiffness, then the subject was put back in the cast in the early afternoon after an average of eighteen hours out of the cast.)

Girth of the upper and lower arms, thighs and calves were measured at standard distances from bony prominences twice weekly in the first pair of subjects, using a narrow, steel tape measure. In an effort to overcome the source of error resulting from variable tension on the tape measure, a device was made consisting of an encircling 1½ inch wide metal band, with tape measure rivited along one edge; the band was mounted on a standard in such a way that 2 (and 5) pound weights could be hung from the metal band's free end in order to produce a constant tension. With this device (used for the measurement of calf and thigh circumference on the second pair of subjects), measurements of the circumference of the calf could be closely checked by different observers (standard deviation over four control weeks equaled ± 2.4 mm. or 0.67 per cent.) Measurements were made after subjects had been lying down not less than thirty minutes in order to measure the leg when in a constant state. Measurements of the circumference of the legs showed a gradual decline over the first thirty to forty minutes after the assumption of the horizontal position before reaching measurements approximating those found in the morning basal state.

The reaction of the circulation to the upright position in prolonged motionless standing was studied by the tilt table test which has enjoyed increasing favor in recent years as a measure of the "fitness" of the circulatory system.⁴⁰⁻⁴² The subject lay quietly in the horizontal position on the tilt table for twenty-five to forty minutes during which pulse rate and blood pressure readings were taken every two to four minutes. The pulse rate and blood pressure usually became well stabilized within twenty minutes. The table was then tilted slowly over a period of thirty seconds to an angle of 65 degrees, feet down, the subject adjusting his feet on the footboard at that time if necessary; thereafter, the subject stood motionless and unsupported with arms at his side, his weight being borne mainly by his heels against the footboard. Pulse rate and blood pressure readings were made every one to two minutes with the subject in this position. The subject remained in the tilted position for

twenty minutes, unless fainting occurred in a shorter interval. During a number of tilt table tests electrocardiograms (three standard leads) and measurements of the girth of the right calf and thigh were taken before, during and following tilting. During the immobilization period

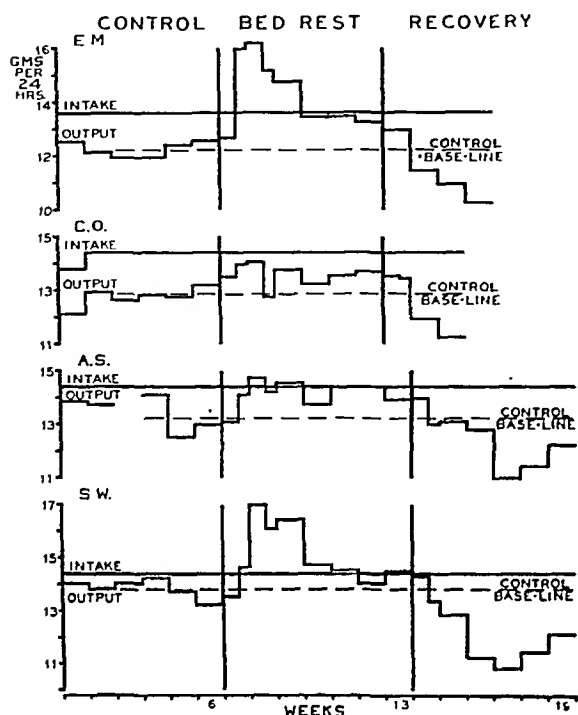


FIG. 1. Effect of immobilization on the nitrogen metabolism of four normal male subjects. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase. For each subject the control base-line is an average of the total outputs of the last four control weeks. The nitrogen outputs of the first two weeks of immobilization and of the first recovery week have been charted in four- and three-day periods in order to indicate the duration of the delay in the increase in nitrogen excretion during immobilization, the peak of nitrogen excretion during immobilization and the delay in the fall in nitrogen excretion during recovery.

the subjects were taken out of their casts thirty minutes prior to the test. Tests were performed at the same time of day (3 P.M.) and under relatively constant temperature conditions.

Blood volume determinations were made employing the Evans blue (T-1824) method of Gregersen, Gibson and Stead⁴³ as outlined by Gibson, Evans and Evelyn.^{44,45} Hematoerits were determined by the Wintrobe tube, and centrifugation was carried out for sixty minutes at 3,000 r.p.m. Hematocrits were corrected by allowing 8.5 per cent for the per cent of the observed cell volume as plasma trapped between red cells.⁴⁶ A dye standard was prepared for

each blood volume determination from the ampule of dye used for injection. Possible hemolysis in the serum samples containing dye was corrected by the formula of Gibson and Evelyn.⁴⁵

At the time of withdrawal of blood for the serum blank, blood was also withdrawn for coagulation time determinations by the method of Lee and White. Test tubes of Wassermann tube size (1.1 cm. diameter) were used which give coagulation times in normals that are somewhat longer than those obtained with the standard tube 8 mm. in diameter.⁴⁷ Coagulation times of the subjects during the control periods were eight to eleven minutes. At the conclusion of the blood volume determinations circulation times were measured, employing deeholin and maeasol.⁴⁸

The Master two-step test⁴⁹ and the Schneider test^{50,51} were used as indices of physical fitness. Using the Master test in the first subject E. M., the maximum number of climbs was determined following which the pulse rate and systolic blood pressure returned to within ten points of the resting level within two minutes; in the other three subjects, the number of climbs was kept constant for each subject and the varying response of pulse and systolic pressure noted. The Schneider index was selected because it can be performed without undue effort by a convalescent able to stand and step up on an 18-inch step. As often as possible, tests were performed at the same time of day (4 P.M.).

Tests of respiratory function included vital capacity, ventilation at rest per minute and maximum ventilation capacity per minute⁵² employing a calibrated 85 liter capacity Tissot gasometer. Ventilation per minute at rest was taken as the average of two, five-minute periods under basal conditions. Maximum ventilation capacity per minute was taken as the average of two, thirty-second runs. Determinations were also made of breath-holding time and of the behavior of the pulse during breath-holding against a 40 mm. column of mercury (Flack or "persistence" test^{53,54}).

X-rays of the long bones and spine of the first pair of subjects were made at intervals under exactly duplicated x-ray technic in an effort to detect possible bone rarefaction resulting from immobilization.

Observations were made of the resting pulse rate and blood pressure before, during and following immobilization. Measurements made during tests carried out in the morning basal

state make up a large proportion of the data of this comparative study.

RESULTS

A. Chemical Studies. 1. *Nitrogen:* (Fig. 1.) During the control periods the subjects maintained small positive nitrogen balances

variations from the control base line have been employed for the calculation of total losses throughout the nitrogen and mineral balance studies.

During immobilization all four subjects showed an increase in nitrogen excretion

TABLE II
DELAY IN THE INCREASE IN NITROGEN EXCRETION DURING IMMOBILIZATION; DAILY URINARY NITROGEN AND DAILY TOTAL (URINARY PLUS FECAL) NITROGEN EXCRETION DURING FIRST TEN DAYS OF IMMOBILIZATION

	Subject E. M.		Subject C. O.		Subject A. S.		Subject S. W.	
	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.
Average of last four control weeks...	11.35	12.21	11.59	12.87	11.45	13.24	12.68	13.82
Average deviation of daily output from average of last four control weeks.....	±0.90	±0.76	±0.65	±0.64	
Immobilization period								
Day 1.....	13.65*	14.54*	12.60	13.89	10.53	12.61	11.90	12.97
2.....	11.69	12.58	12.35	13.64	10.80	12.88	12.88	13.95
3.....	11.37	12.26	12.50	13.79	11.30	13.38	12.72	13.79
4.....	12.70	13.59	11.45	12.74	11.50	13.58	12.50	13.57
5.....	75.89†	76.78	11.42	12.71	11.80	13.88	10.99	12.06
6.....	13.60	14.49	14.20	15.49	12.03	14.11	13.82	14.89
7.....	15.70	16.59	12.42	13.71	12.25	14.33	15.70	16.77
8.....	15.30	16.42	12.18	13.39	13.20	14.97	16.02	17.18
9.....	16.20	17.32	11.95	13.16	12.75	14.46	14.85	16.01
10.....	14.90	16.02	14.20	15.41	13.79	15.50	16.95	18.11

* High urinary creatinine on this day and low creatinine on preceding day suggests that this represents more than a twenty-four-hour sample.

† Figures in italics indicate the first day of significant increase in nitrogen excretion.

with the output relatively constant. The total outputs of the last four control periods were averaged to obtain the control base line. This is drawn on the graph as an interrupted line to demonstrate clearly the deviations of nitrogen excretion during the immobilization and recovery periods from that of the control period. Each subject established his own distinctive balance with respect to intake so that in assessing the effect of immobilization upon nitrogen excretion, displacements from a control base line are of greater significance than balances related to intake. Displacements or

which was reflected principally in the urinary nitrogen. The fecal nitrogen remained relatively constant throughout all phases of the experiment. During the first four days of immobilization there was little change in the output; a rather abrupt rise then occurred generally on the fifth or sixth day. This delay (Table II) of four or five days is in contrast to the immediate excessive excretion of nitrogen in response to fever and the delay of only one day following trauma. The peak of nitrogen excretion occurred during the second week. The extent of nitrogen loss varied considerably

in the several subjects and could not be correlated with body type. During the recovery phase nitrogen excretion remained high for a few days and then fell rapidly to reach the control level by the second week. The output continued to decrease, falling

losses among the four men was 53.7 Gm., equivalent to 1.7 Kg. of muscle protoplasm.

2. *Calcium*: During the control periods the subjects remained in positive calcium balance. During immobilization there was an increase in both urinary and fecal cal-

TABLE III

NITROGEN METABOLISM—TOTAL NITROGEN LOSSES DURING IMMOBILIZATION, TOTAL RETENTION DURING RECOVERY AND MAXIMUM DEVIATION FROM CONTROL BASE-LINE (AVERAGE OF LAST FOUR CONTROL WEEKS)

I. Immobilization

Subject	Control	Immobilization Period							
	Average Daily Balance (last 4 wk.), Gm.	No. of Wk.	Average Daily Balance, Gm.	Average Daily N Loss, Gm.	Total N Loss (entire period), Gm.	Total N Loss (first 2 wk.), Gm.	Total N Loss (first 3 wk.), Gm.	Maximum Deviation from Control Base-line	
								Week of Occurrence	Deviation, Gm./day (for the week)
E. M.	+1.36	6	-0.63	1.99	83.6	40.3	58.3	2nd	-3.55
C. O.	+1.54	6	+0.83	0.71	29.8	10.3	16.7	3rd	-0.91
A. S.	+1.18	7	+0.25	0.93	45.6	11.0	20.2	3rd	-1.32
S. W.	+0.60	7	-0.54	1.14	55.9	20.7	38.4	2nd	-2.78

II. Recovery

Subject	No. of Weeks	Average Daily Balance, Gm.	Average Daily N Gain, Gm.	Total N Retention, Gm.	Maximum Deviation from Control Base-line	
					Week of Occurrence	Deviation, Gm./day (for the week)
E. M.	4	+2.15	0.79	22.1	4th	+1.95
C. O.	3	+2.18	0.64	13.4	3rd	+1.63
A. S.	6	+2.05	0.87	36.5	4th	+2.24
S. W.	6	+2.34	1.74	73.1	4th	+2.97

below control levels so that nitrogen was then being stored. Maximum storage or retention occurred at the fourth recovery week. In the two subjects studied for six weeks in recovery, nitrogen excretion was again approaching control levels by the end of the sixth week.

The total nitrogen losses during immobilization ranged from 29.8 Gm. to 83.6 Gm. (Table III.) The average of the total nitrogen

cium excretion. The increase in fecal calcium excretion was variable but generally progressive, fecal calcium being greatest during the latter weeks of bed rest.

Urinary calcium excretion began to increase on the second or third day of bed rest, that is, slightly preceding the increase in nitrogen excretion, and climbed gradually, reaching a peak by the fourth to fifth week. This high level of urinary excretion

was more than double the control period levels in all four subjects and was maintained in a more or less plateau manner similar to that described by Howard⁵⁵ in patients with fractures. The maximum excretion in the urine ranged from 140 to 594 mg. per day (for a three to four-day pool) with an average maximum of 342.

Calcium excretion (urinary and total) decreased slowly in recovery, continuing to exceed control levels during the first three weeks. Calcium excretion continued to decrease thereafter, minimum excretion occurring during the fifth and sixth recovery weeks in the two subjects studied for this length of time. Subject S. W. exhibited marked calcium retention during the fifth and sixth weeks in recovery and had not returned to control levels at the end of the sixth week.

The pattern and extent of the calcium changes are shown in Figure 2 and Tables iv and v. Total calcium losses ranged from 8.95 to 23.9 Gm. and averaged 14.1 Gm. (These calculations include the first three recovery weeks since calcium excretion still exceeded control levels during that time.)

Among the factors that influence the solubility of urinary calcium are urine volume, urinary pH and urinary citric acid concentration. The importance of the dilution factor and of acidity of the urine in

favoring calcium solubility is well recognized. The significance of urinary citric acid has been more recently appreciated; this influence resides in the formation of the weakly ionized and very soluble calcium citrate complex. Some evidence for the

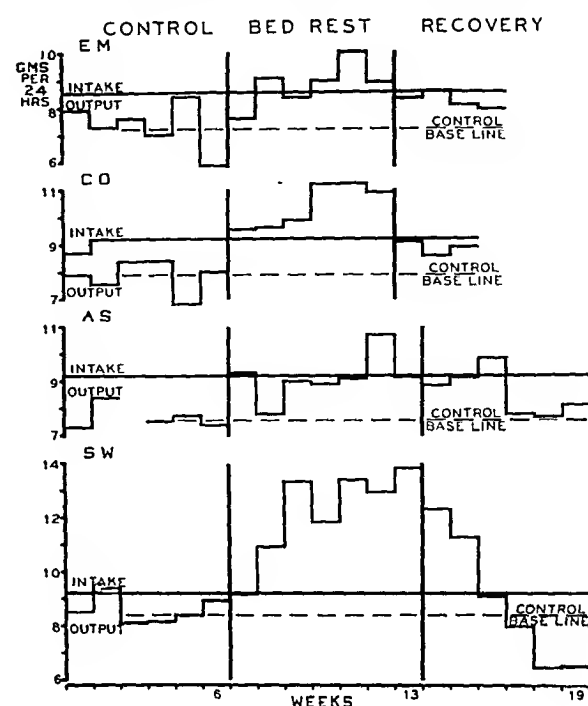


FIG. 2. Effect of immobilization on the calcium metabolism of four normal male subjects.

protective action of citric acid has been shown by Shorr, Almy, Sloan, Taussky and Toscani⁵⁶ in ambulatory patients in whom

TABLE IV

CALCIUM METABOLISM—TOTAL CALCIUM LOSSES RESULTING FROM IMMOBILIZATION AND MAXIMUM DEVIATION FROM CONTROL BASE-LINE (AVERAGE OF LAST FOUR CONTROL WEEKS)

Subject	Control	Immobilization						Recovery	Total Calcium Loss, Gm.
	Average Daily Balance, (last 4 wk.), Gm.	No. of Wk.	Average Daily Balance, Gm.	Average Daily Ca Loss, Gm.	Total Loss in Immo- bilization, Gm.	Maximum Deviation from Control Base-line		Additional Ca Loss (first 3 wk.), Gm.	
						Week of Occur- ence	Deviation, Gm./day (for the wk.)		
E. M.	+0.131	6	-0.028	0.159	6.68	5th	-0.280	2.27	8.95
C. O.	+0.130	6	-0.118	0.248	10.42	5th	-0.329	2.04	12.46
A. S.	+0.162	7	+0.006	0.156	7.65	6th	-0.312	3.59	11.24
S. W.	+0.081	7	-0.299	0.380	18.62	7th	-0.543	5.25	23.87

TABLE V
CHANGES IN URINARY CALCIUM EXCRETION RESULTING FROM IMMOBILIZATION

Subject	Control	Immobilization						
	Control Base-line Urinary Calcium, Gm./day	No. of Wk.	Average Daily Urinary Calcium, Gm.	Average Daily Urinary Calcium Loss (above control base-line), Gm.	Total Urinary Calcium Loss (above control base-line), Gm.	Maximum Urinary Calcium		
						Wk. of Occurrence	Maximum for Week, Gm./day	Deviation from Control Base-line, Gm./day
E. M.	0.050	6	0.102	0.052	2.18	4th	0.119	0.069
C. O.	0.116	6	0.284	0.168	7.06	6th	0.335	0.219
A. S.	0.123	7	0.212	0.089	4.36	6th	0.249	0.126
S. W.	0.213	7	0.515	0.302	14.80	5th	0.577	0.364

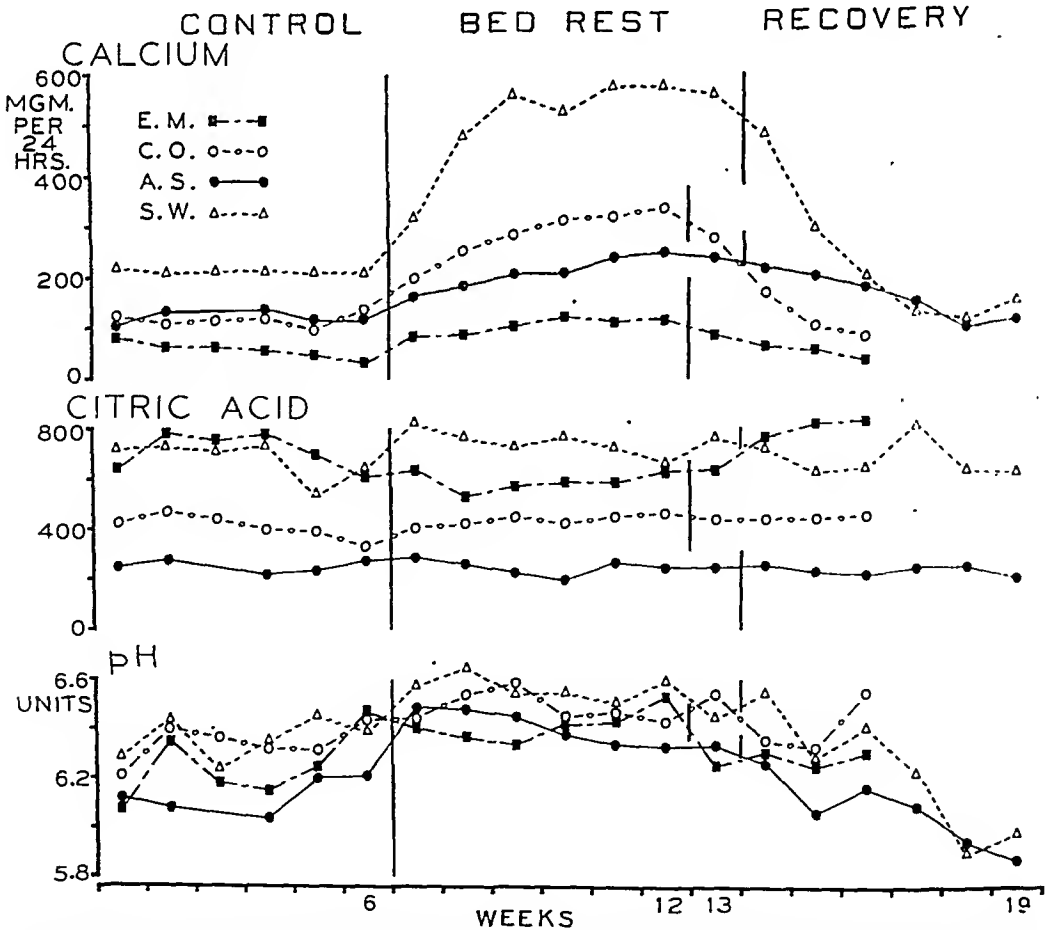


FIG. 3. Effect of immobilization on the urinary excretion of calcium and citric acid and on urinary pH in four normal male subjects. Daily calcium intake was 0.852 Gm. for subject E. M., 0.920 Gm. for subjects C. O., A. S. and S. W.

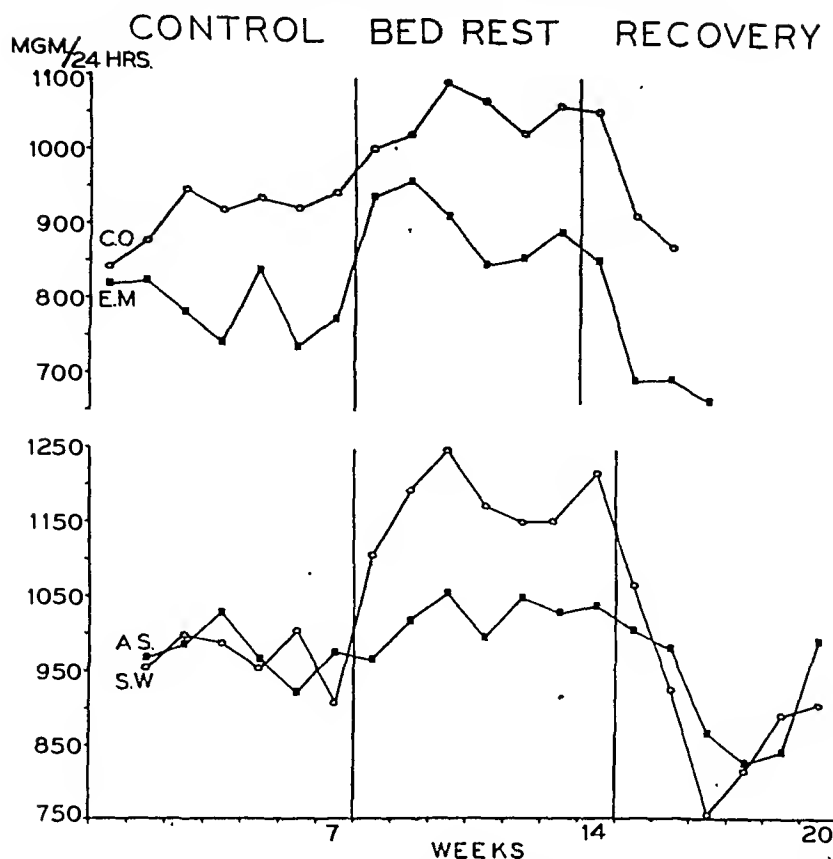


FIG. 4. Effect of immobilization on the urinary excretion of phosphorus of four normal male subjects. Daily phosphorus intake was 1.50 Gm. for subject E. M., 1.64 Gm. for subjects C. O., A. S. and S. W.

variations in calcium excretion are paralleled by proportional variations in the excretion of citric acid.

Despite the fact that urinary calcium levels were doubled, factors influencing urinary calcium solubility showed little or no change. During immobilization urine volumes increased only slightly, the average daily urine volumes averaging 235 cc. higher during immobilization than during the control period. The urinary pH rose between 0.1 and 0.2 units during immobilization. The citric acid excretion failed to show any compensatory rise. (Fig. 3.) No red blood cells or calcium phosphate crystals were found in frequent microscopic examinations of the urines.

3. *Phosphorus*: During the control periods the subjects remained in positive phosphorus balance. During immobilization there was an increase in both urinary and fecal phosphorus excretion, the increase in fecal phosphorus being small and variable. Uri-

nary phosphorus excretion (Fig. 4) began to increase during the first week of immobiliza-

TABLE VI
PHOSPHORUS METABOLISM—TOTAL PHOSPHORUS LOSSES
RESULTING FROM IMMOBILIZATION AND MAXIMUM
DEVIATION FROM CONTROL BASE-LINE (AVERAGE
OF LAST FOUR CONTROL WEEKS)

Subject	Control	Immobilization					
	Average Daily Balance (last 4 wk.), Gm.	No. of Weeks	Average Daily Balance, Gm.	Average Daily Loss, Gm.	Total Loss in Immobilization, Gm.	Maximum Deviation from Control Base-line	
						Week of Occurrence	Deviation, Gm./day (av. for the wk.)
E. M.	+0.328	6	+0.058	0.270	11.34	2nd	-0.373
						5th	-0.319
C. O.	+0.278	6	+0.145	0.133	5.60	4th	-0.188
A. S.	+0.245	7	+0.129	0.116	5.69	3rd	-0.125
						6th	-0.243
S. W.	+0.169	7	-0.070	0.239	11.70	3rd	-0.370
						7th	-0.356

tion and reached a peak at the second to third week; this peak coincided rather closely with the peak of nitrogen excretion. Urinary phosphorus then decreased somewhat but demonstrated a second peak of excretion at the sixth to seventh week. This

measured phosphorus losses in each subject were as follows: The theoretical phosphorus loss exceeded the measured phosphorus loss by 19.5 per cent for C. O., 14.5 per cent for A. S. and 5.1 per cent for S. W.; for E. M. the theoretical phosphorus loss

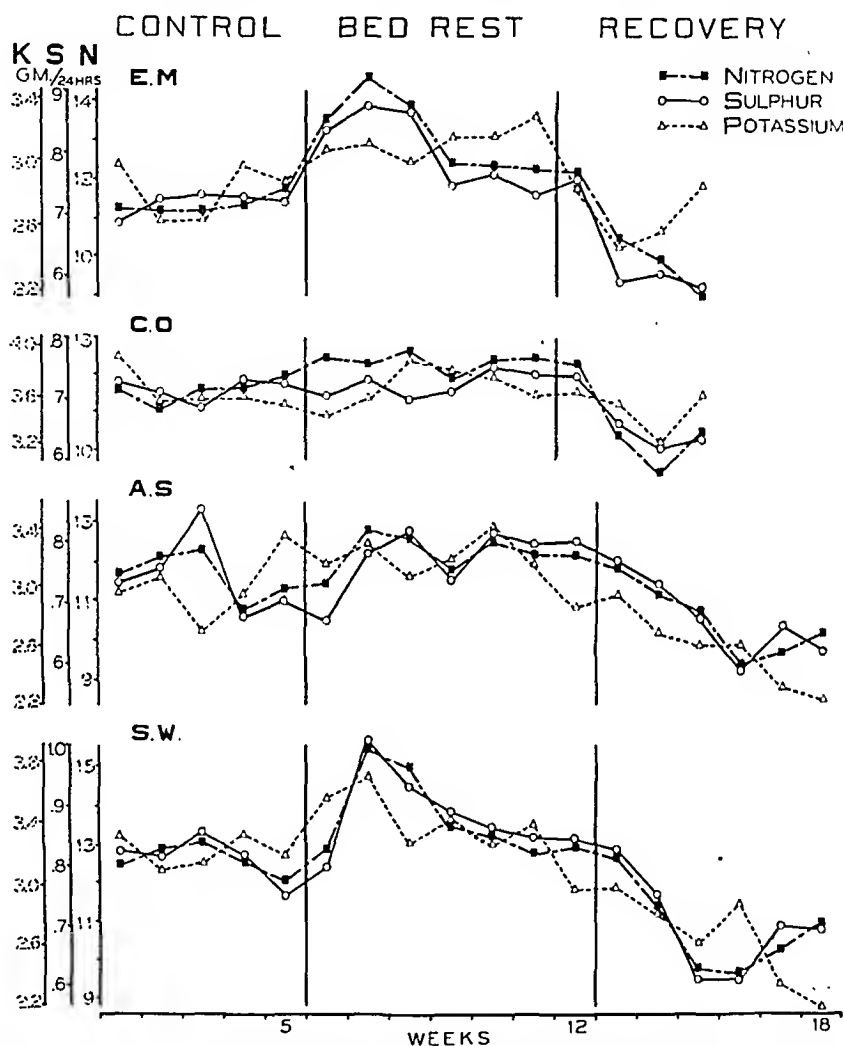


FIG. 5. Effect of immobilization on the urinary excretion of nitrogen, total sulfur and potassium of four normal male subjects.

second peak occurred at a time when calcium excretion was at its highest level. In recovery, urinary phosphorus fell rapidly and phosphorus retention took place during the third, fourth and fifth recovery weeks. Excretion returned to control levels in the sixth recovery week.

Total phosphorus losses ranged from 5.6 to 11.6 Gm. (Table VI.) Discrepancies between theoretical phosphorus losses (calculated from nitrogen and calcium) and

was 23.4 per cent less than the measured loss. There was fairly good agreement from week to week between measured and theoretical phosphorus losses.

4. *Total sulfur*: The average ratio of urinary total sulfur to urinary nitrogen in the four subjects during the last five control weeks was 1:15.8. This ratio of sulfur to nitrogen was maintained quite constantly throughout the immobilization and recovery periods. (Fig. 5 and Table VII.)

The sulfur in these ratios is slightly less than in the generally accepted sulfur-nitrogen ratio of muscle of 1:14. However, the close correlation of the sulfur excretion with nitrogen from week to week during immobilization suggests a sulfur-rich source of the excreted nitrogen, presumably muscle.

was only 5 to 8 per cent and the day to day coffee intake was quite constant.

During the control period the subjects were approximately in potassium equilibrium. During immobilization potassium excretion increased, total losses based on variations from control base line excretion

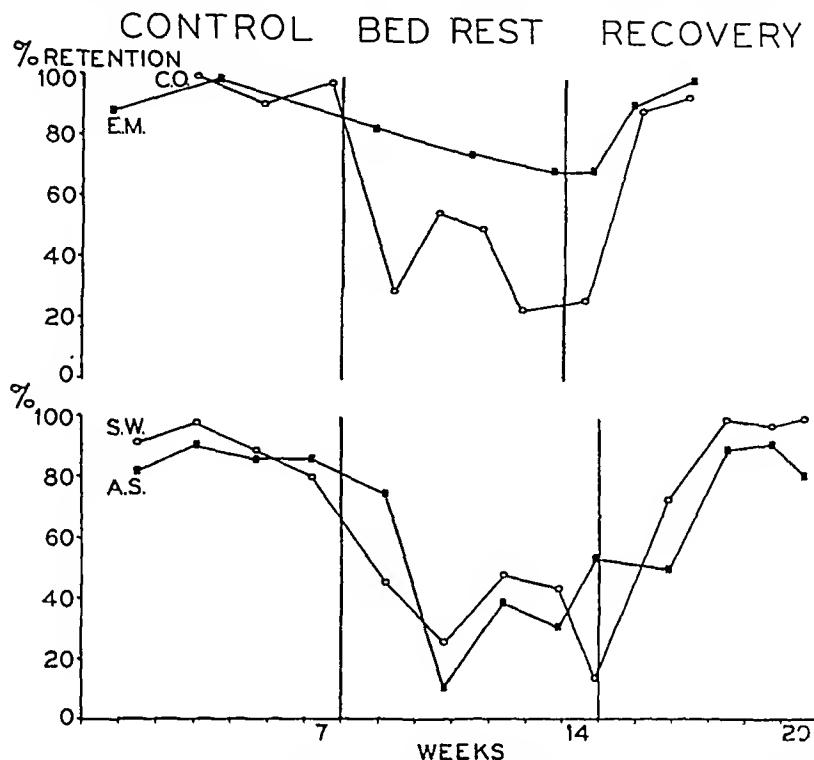


FIG. 6. Effect of immobilization on the percentage of fed creatine retained in creatine tolerance tests in four normal male subjects. The test dose of creatine was 1.32 Gm.

5. *Potassium*: Potassium balance data were not strictly accurate because of minor variations in the daily potassium intake. The discovery that ordinary beverage coffee contains appreciable amounts of potassium (89 mg. per 100 cc. by our analysis, 88 mg. per 100 cc. by McCance and Widdowson¹⁶ in a five-minute infusion), made it evident that the daily intake was actually 200 to 300 mg. higher than was indicated from the diet analyses. This additional potassium intake from coffee was estimated to be 0.25 Gm. and this value was added to the potassium intake figures. The general conclusions regarding the effect of immobilization upon potassium metabolism are believed not to be invalidated because the increase in potassium intake from coffee

ranging from 4.2 to 14.2 Gm. The increase in potassium excretion occurred only in the urine (Fig. 5), fecal potassium remaining unchanged. In recovery, all four subjects developed positive potassium balances and in the two subjects studied for six weeks in recovery, potassium balances were still strongly positive at the sixth week. The total amounts of potassium retained by these two subjects in six weeks recovery more than doubled the amounts they lost during immobilization.

6. *Sodium*: Sodium balances were carried out on the second pair of subjects. The total sodium excretion was slightly increased during immobilization and fell slightly below control levels during recovery. The principal change occurred in urinary sodium;

actually, the amounts of sodium in the feces (which were less than 0.2 Gm. daily) tended to be reduced during immobilization.

In the first subject (A. S.), the sodium balance was +0.46 Gm. per day during control, shifted to +0.17 during immobili-

a considerable fall during immobilization. (Fig. 6.) All control period tests showed greater than 80 per cent retention (well within the normal range). During immobilization there was a gradual fall in retention, the minimum ranging from 11 to 70 per

TABLE VII
RATIO OF URINARY NITROGEN TO URINARY TOTAL SULFUR

Periods	Subject E. M.			Subject C. O.			Subject A. S.			Subject S. W.		
	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio
Control—last four weeks	11.12	.724	15.38	11.20	.708	15.83	12.84	.815	15.76
	11.11	.733	15.16	11.57	.685	16.89	12.31	.854	14.42	13.08	.856	15.29
	11.36	.726	15.66	11.68	.720	16.23	10.73	.683	15.70	12.68	.815	15.56
	11.79	.721	16.34	11.92	.725	16.46	11.32	.705	16.07	12.10	.750	16.12
Average of control weeks	11.35	.726	15.64	11.59	.710	16.35	11.45	.747	15.40	12.67	.809	15.68
Immobilization												
1st wk	13.51	.837	16.17	12.42	.707	17.58	11.46	.673	17.03	12.93	.798	16.21
2nd wk	14.62	.877	16.68	12.29	.731	16.80	12.80	.783	16.34	15.44	1.010	15.30
3rd wk	13.86	.875	15.84	12.57	.698	18.00	12.70	.816	15.57	15.04	.933	16.12
4th wk	12.44	.747	16.67	11.97	.711	16.84	11.83	.740	16.00	13.56	.887	15.30
5th wk	12.37	.765	16.17	12.38	.753	16.43	12.68	.817	15.52	13.30	.857	15.52
6th wk	12.32	.732	16.83	12.47	.740	16.86	12.21	.796	15.34	12.70	.848	14.98
7th wk	12.18	.805	15.13	13.04	.843	15.48
Recovery												
1st wk	12.04	.757	15.92	12.33	.738	16.72	11.87	.768	15.44	12.68	.829	15.30
2nd wk	10.49	.590	17.78	10.38	.662	15.70	11.22	.733	15.33	11.47	.753	15.24
3rd wk	9.96	.605	16.47	9.45	.622	15.20	10.78	.680	15.84	9.81	.610	16.06
4th wk	9.07	.580	15.62	10.46*	.636	16.44	9.32	.593	15.69	9.62	.612	15.72
							9.69	.663	14.60	10.28	.700	14.70
							10.22	.620	16.52	10.99	.693	15.86

* 4 days.

zation and to +0.71 in recovery. In the second subject (S. W.), sodium balance was +0.16 Gm. per day in control, -0.02 during immobilization and +0.34 in recovery.

7. *Creatine metabolism*: Urinary creatinine excretion remained quite constant throughout all periods of study. There were day to day fluctuations at a low level in creatine excretion (dietary intake was not creatine-free) but no significant shifts occurred from one period of study to the next. However, tests of creatine tolerance showed

cent with an average minimum retention of 29 per cent. During recovery the tests gradually improved and reached normal levels at the end of the third week.

8. *17-ketosteroids*: Changes in 17-ketosteroid excretion varied considerably from subject to subject. (Table VIII.) One subject (E. M.) showed a variable fall in 17-ketosteroids during immobilization which appeared to be significant. Two subjects (C. O. and S. W.) showed small increases during immobilization. The increase in

S. W. is probably significant; in C. O. it is questionable. The fourth subject (A. S.) showed a fairly constant 17-ketosteroid excretion throughout the experiment. During recovery no significant changes took place other than a gradual return to control levels of excretion.

variation in the excretion values throughout the study and by the irregular appearance of equally high peaks of excretion during both the control and immobilization phases. There was no apparent correlation between the excretion of glycogenic corticoids and nitrogen or 17-ketosteroids.

TABLE VIII
URINARY 17-KETOSTEROID EXCRETION (ANALYSES OF SEVEN-DAY POOLED URINE SPECIMENS)
AND COMPARISON WITH TOTAL NITROGEN EXCRETION

Periods	Subject E. M.		Subject C. O.		Subject A. S.		Subject S. W.	
	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day
Control—last six weeks	9.50	12.52	11.70	12.13	13.86	14.03
	11.00	12.13	9.62	12.92	8.85	13.75	8.10	13.82
	10.98	11.95	9.80	12.66	9.65	14.04
	10.90	11.94	9.85	12.82	9.55	14.13	8.82	14.27
	11.90	12.39	10.10	12.78	9.27	12.55	9.20	13.74
	10.65	12.55	9.52	13.23	9.90	13.04	10.70	13.22
Average of last four control weeks...	11.11	12.21	9.82	12.87	9.57	13.24	9.59	13.82
Immobilization								
1st week.....	9.88	14.40	9.26	13.71	10.32	13.54	10.01	14.00
2nd week.....	8.55	15.74	10.90	13.50	10.34	14.51	12.39	16.60
3rd week.....	8.95	14.77	12.25	13.79	9.85	14.56	12.10	16.35
4th week.....	6.02	13.45	10.05	13.23	9.42	13.75	11.45	14.74
5th week.....	10.50	13.47	12.32	13.56	8.12	14.43	11.30	14.52
6th week.....	7.10	13.27	11.88	13.73	9.40	14.43	11.90	14.02
7th week.....	9.22	13.93	12.10	14.48
Average of immobilization period	8.50	14.18	11.11	13.59	9.52	14.16	11.61	14.96
Recovery								
1st week.....	7.44	12.94	10.14	13.51	8.83	13.59	11.97	13.90
2nd week.....	9.16	11.46	9.77	11.96	9.25	13.09	9.70	12.86
3rd week.....	9.50	10.95	10.40	11.25	10.98	12.79	10.50	11.24
4th week.....	11.00	10.24	11.70*	8.93	11.00	9.15	10.85
5th week.....	8.50	11.46	8.08	11.46
6th week.....	9.42	12.26	9.20	12.14
Average of recovery period.....	9.27	11.40	10.36	12.24	9.32	12.36	9.77	12.07

* 4 days.

9. *Adrenal corticoids* (by Dr. Konrad Do-briner): During the first three weeks of immobilization in both subjects there was a definite although variable increase in urinary corticoids. Interpretation is complicated, however, by the considerable

10. *Other factors in the urine*: During the last four control weeks the average daily urinary output among the four subjects was 1,684 cc., during immobilization 1,919 cc. and 1,819 cc. during the first four recovery weeks. The daily fluid intake was not fixed

but the subjects were asked to take a minimum of 2,000 cc. The intake actually ranged between 2,000 and 2,400 cc. throughout all periods of study and averaged 2,069 cc. during control, 2,051 cc. during immobilization and 2,140 cc. during recovery.

performed at weekly intervals throughout the experiments showed a decline during immobilization, ranging from 1.0 to 4.3 calories per sq. m. per hour, averaging 2.4. This represents a reduction in basal heat production or oxygen consumption ranging

TABLE IX
EFFECT OF IMMOBILIZATION UPON SERUM CALCIUM LEVELS

Subject	Control		Last Four Immobilization Weeks and First Two Recovery Weeks					Recovery	
	No. of Determinations	Range and Average of last 4 Wk., mg./100 cc.	No. of Determinations	Range and Average Value, mg./100 cc.	No. of Determinations higher than 11.5 mg./100 cc.	Maximal Serum Ca Value, mg./100 cc.	Week of Occurrence of Maximal Value	No. of Determinations	Range and Average of last 4 Wk., mg./100 cc.
E. M.	5	11.2 (11.0-11.4)	8	11.6 (10.9-12.0)	4	12.0	5th immobilization	2	11.1 (10.6-11.7)
C. O.	5	10.9 (10.5-11.6)	8	11.4 (9.5-12.7)	3	12.7	1st recovery	1	10.5
A. S.	2	11.0 (10.7-11.2)	5	11.8 (11.1-12.3)	4	12.3	2nd recovery	2	10.9 (10.8-11.0)
S. W.	2	10.5 (10.2-10.8)	5	11.9 (10.7-12.6)	2	12.6	2nd recovery	2	10.9 (10.2-11.7)

There were no significant alterations in urinary specific gravity measured daily throughout the experiments.

11. *Blood chemistry studies:* There were no significant changes during the experiments in the blood levels of total proteins, phosphorus, sodium or potassium.

During the last three weeks of immobilization and first two recovery weeks two or more serum calcium levels in each of the four subjects were found to be higher than the generally accepted high normal value of 11.5 mg. per cent. (Table ix.) The maximum serum calcium levels in three of the subjects were 12.7 (C. O.), 12.3 (A. S.) and 12.6 (S. W.) mg. per cent; these maximum values were all found in the second recovery week. In A. S. and S. W., single values of 11.9 mg. per cent were found early in the control period. The maximum serum calcium value in E. M. was 12.0 mg. per cent and occurred in the fifth immobilization week.

B. Physiological Studies. 1. *Basal metabolism:* Tests of the basal metabolic rate

from 3.1 to 11.5 per cent, averaging 6.9 per cent. In recovery, the basal metabolic rate returned to control levels within three to four weeks.

2. *Muscle strength:* Tests on the ergometer showed decreases in muscle strength during immobilization; these decreases were more marked in the immobilized leg muscles than in the other muscle groups tested.

Strength of the biceps muscle groups tested by the flexed arm pull showed an average decline among the four subjects of 6.6 per cent. Strength of the shoulder and arm muscles tested by the straight arm pull showed an average decline of 8.7 per cent. Decline in the strength of the anterior tibial muscle groups in the foot pull ranged from 7.8 to 20.6 per cent with an average decline of 13.3 per cent. Decline in the strength of the gastrocnemius-soleus muscle groups ranged from 11.8 to 31.0 per cent with an average decline of 20.8 per cent. In recovery, it required approximately four weeks for muscle strength to return to

control levels. Measurements of the strength of the grip and of abdominal and back muscles revealed no significant decreases at the end of the immobilization period.

3. *Girth of extremities:* In the first pair of subjects, measurements were made of the girth of the arms. The decrease in girth resulting from immobilization amounted to approximately 2 per cent for both upper arms and forearms.

Measurements of the girth of the thighs and calves were made in all four subjects, a more accurate measuring device being employed in the second pair. In the first pair of subjects, the decrease in the circumference of the thighs was 5.0 per cent for E. M. and 2.1 per cent for C. O. In the second pair of subjects the decrease in the circumference of the thighs was 3.6 per cent for A. S. and 4.8 per cent for S. W.

Decreases in the circumference of the calves were 5.5 and 6.0 per cent respectively in the first pair of subjects and 5.6 and 6.3 per cent in the second pair. When these decreases in the girth of the calves are transposed into decreases in the cross sectional area, a better conception of the extent of muscle atrophy is obtained; the decreases in the cross sectional area amounted to 4.2 to 10.0 per cent for the thighs and 9.7 to 12.5 per cent for the calves. If it is supposed that no appreciable volume decreases were occurring in any structure in the legs other than muscle, it is evident that an appreciable extent of muscle atrophy took place.

In the recovery period, five to six weeks was required for the legs to return to their original circumference.

4. *Tilt table:* Immobilization brought about a definite deterioration in the mechanisms essential for adequate circulation in the erect position. Within one week of the time immobilization was instituted, there began to develop an increasing tendency of the subjects to faint during tilt table tests.

Analysis of tilt table tests and correlation of data on pulse rate and blood pressure with the observed general reactions of the

subject, indicated that the pulse pressure was the most important factor involved in the response of the circulation to tilting. With the subject standing in the upright position on the tilt table, it was found that when the pulse pressure became reduced to between 10 and 12 mm. of mercury a critical level was reached at which circulation became impaired, dizziness and pallor appeared and fainting followed shortly thereafter. The degree of change in pulse pressure also correlated closely with the subjects' reactions. Next in importance were fall in systolic pressure and degree of change in pulse rate. Graybiel and MacFarland,⁴¹ in an analysis of tilt table tests on ninety-one normal individuals, concluded that pulse pressure and fall in systolic pressure were the most important factors denoting a failing circulation.

Figure 7 shows the percentage change from the resting levels of pulse rate and pulse pressure, resulting when the subjects were tilted to 65 degrees feet downward for twenty minutes. A normal, healthy individual accustomed to upright activity (as exemplified by our subjects during the control period), when tilted for twenty minutes will exhibit an increase in pulse rate and decrease in pulse pressure of 40 to 70 per cent from levels obtained in the resting horizontal position. The graph shows that during immobilization the changes in pulse rate and pulse pressure on tilting became more marked (generally greater than 70 per cent) and an increased frequency of fainting in tilt table tests developed. For one subject (S. W.), who fainted during nearly every test, the method of charting has been altered so that the minutes required to faint are plotted on the ordinate line. During immobilization this subject fainted at much shorter intervals of time.

Toward the end of the immobilization period all four subjects developed purpuric hemorrhages about the feet and ankles in the tilt table tests. These hemorrhages extended to the knees in one subject and to the mid-thigh in another. (Platelets were abundant in the blood smears throughout the

experiment. The prothrombin time was not altered significantly. The Rumpel-Leeds tourniquet test on the arm was normal. The average daily vitamin C intake was 144 mg.)

Some of the underlying factors in this circulatory deterioration during immobili-

of the immobilization period when S. W. was fainting during tilt table tests consistently after six minutes, tilt table tests were performed on four successive days. On the first and third days, tests were performed with his legs wrapped firmly in Ace ban-

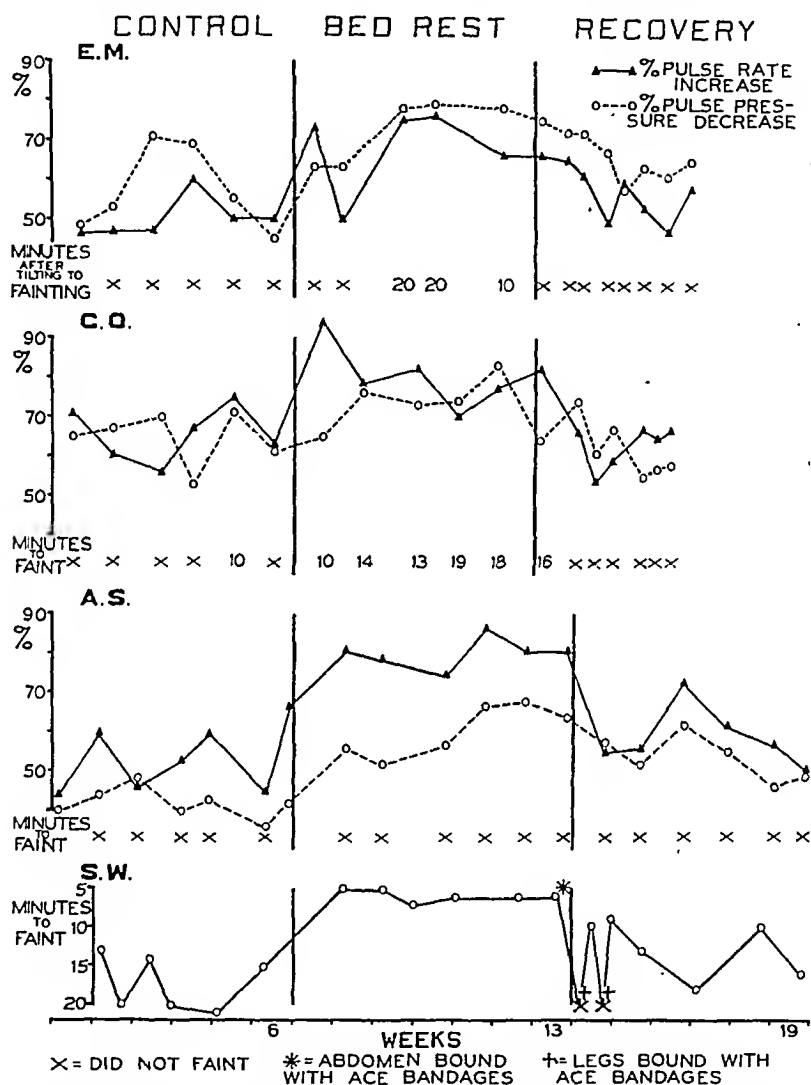


FIG. 7. Effect of immobilization on the responses of pulse rate and pulse pressure to tilting to 65 degrees feet downward for twenty minutes in four normal male subjects. The chart also shows for each test the number of minutes in the tilted position required for fainting to occur; an "x" indicates that on that test the subject remained in the tilted position for more than twenty minutes without fainting. For subject S. W., who fainted on nearly every test, the method of charting has been altered so that minutes required for fainting to occur are plotted on the ordinate line.

zation were explored. Experiments carried out on S. W., and shown in Figure 7, would seem to indicate that the legs are probably the principal vascular area in which important changes occur. At the end

dages from the feet to the groin; during these tests he was able to stand for more than twenty minutes without fainting. On the second and fourth days, tests were done in the usual fashion without bandages;

during these tests he fainted in ten and nine minutes. Wrapping the abdomen tightly in Ace bandages had no effect upon the subject's reaction to tilting; during this test S. W. fainted in six minutes.

Measurements of the circumference of the legs during tilt table tests were carried out on the second pair of subjects. Measurements were made in the horizontal position, immediately after assuming the tilted position, at the end of the period of tilting and immediately after resumption of the horizontal position. Differences in these four observations were used to calculate changes in circumference due to (a) venous engorgement and (b) increases in extravascular fluid. In subject A. S., who stood for twenty minutes in all tilt table tests, comparison of the values obtained in control period tests with those of immobilization period tests suggested that during bed rest there was a greater increase in extravascular fluid and a greater progressive increase in venous engorgement than occurred in tests during the control period. In S. W., who fainted much more rapidly on tests during immobilization, a greater increase in extravascular fluid took place during immobilization *within five minutes* of tilting than occurred in thirteen to twenty minutes of tilting in control period tests.

Recovery from the type of circulatory deterioration demonstrated by tilt table tests took place approximately three to four weeks after the subjects became ambulant.

5. *Blood volume:* The decline in plasma volume in the four subjects at the end of three weeks of immobilization ranged from 120 to 320 cc., averaging 191 cc. or 6.3 per cent. Decreases in total blood volume ranged from 180 to 366 cc., with an average decrease of 275 cc. or 5.4 per cent. During the remaining three to four weeks of the immobilization period the blood volume tended to return toward control levels; there was an average increase of 121 cc. in plasma volume and 111 cc. in total blood volume by the end of immobilization. In the recovery period, the plasma and total blood

volumes returned to control levels within three to four weeks.

6. *Circulation time:* Measurements of the speed of the circulation from arm to tongue, arm to perineum and arm to feet by the decholin and macasol methods showed no changes during the immobilization period.

7. *Blood coagulation studies:* Coagulation times by the Lee-White method done on blood from arm veins showed no significant changes as a result of immobilization; indeed, coagulation times tended to be slightly longer during the bed rest period. Prothrombin time determinations, performed on the second pair of subjects, showed a slight prolongation of questionable significance during immobilization.

8. *Exercise tolerance tests:* Master tests, performed in the control period and again in recovery as soon as the subjects were ambulant, showed marked decreases in exercise tolerance as a result of immobilization. Increases in pulse rate and systolic blood pressure after exercise were considerably greater following immobilization. In general, from three to six minutes were required for the pulse and from five to seven minutes for the systolic pressure to return to pre-exercise levels; whereas in control period tests using the same number of climbs, two minutes or less was usually required for the pulse and four minutes or less for the systolic pressure to return to pre-exercise levels.

Schneider tests showed significant declines in scores in all four subjects following immobilization. The average of pre-immobilization scores was +9 points, the average following immobilization was +3. The range of decline in scores was 4 to 9 points, averaging 6 points. Four to six weeks of recovery were required for the Master and Schneider tests to return to control period levels.

9. *Heart size:* X-rays of the chest by standard chest technic, taken every three weeks throughout the studies, showed considerable variation in the apparent size of the heart and no evident tendency toward

reduction in the size of the heart during the immobilization phase.

10. *Electrocardiograms*: There were minor changes during immobilization in electrocardiograms taken with the subjects in the usual resting, horizontal position. The rate was slightly increased and there were minor reductions (1.0 to 1.5 mm.) in the amplitude of the T waves in the second and third leads. No other significant changes were noted which could not be attributed to the slight increase in rate.

Electrocardiograms were made in conjunction with tilt table tests in the second pair of subjects. Records made while the subject was being tilted showed the following changes during the immobilization period: increase in rate in both subjects; slight reduction in the height of R_1 and T_1 and deepening of S_1 in one subject (A. S.) and reduction in height of T_2 in the other subject (S. W.). These changes in the form of the electrocardiogram disappeared during the recovery period.

11. *Resting pulse rate and blood pressure*: During immobilization there was an average increase among the four subjects in resting pulse rate of 3.8 beats per minute, ranging from 1.6 in one subject to 8.3 in another. During the first three weeks of recovery there was an additional average increase of 4.7 beats per minute. From the third recovery week the resting pulse rate declined toward the control level. In the first pair of subjects (recovery period four weeks), the resting pulse rate had not returned to the control level at the end of the fourth week; in the second pair of subjects, the rate had almost returned to the control level at the end of the sixth week. There were no significant changes in the resting arterial blood pressures. It has been supposed that the blood pressure fell during long periods of bed rest; actually, in this experiment systolic blood pressures during immobilization averaged 2.0 mm. higher than the control period resting systolic pressures.

12. *Hematocrits and "blood counts"*: No significant changes attributable to bed rest

occurred in hematocrits or in white cell counts, red cell counts or hemoglobin determinations. In the first pair of subjects, blood volume determinations were performed every two weeks and blood was drawn for chemistry at weekly intervals;

TABLE X
CHANGES IN BODY WEIGHT

Subject	Control	Immobilization		Recovery	
	Weight Change (last 4 wk.), Kg.	No. of Wk.	Weight Change, Kg.	No. of Wk.	Weight Change, Kg.
E. M.	-0.9	6	-1.2	4	+1.3
C. O.	+0.4	6	+1.6	3	+0.8
A. S.	-0.4	7	+1.0	6	+1.9
S. W.	-0.9	7	-0.7	6	+1.1

the estimated average weekly blood loss was 70 cc. This may have contributed to a gradual fall in hematocrit in this pair of subjects throughout the entire four and one-half months of the experiment of 3 volumes per cent in one subject and 4 volumes per cent in the other. In the second pair of subjects on whom blood chemistry and blood volume determinations were done less frequently, there was a gradual fall in hematocrit of 1 and 2 volumes per cent respectively.

13. *Respiration studies*: There were no significant changes during immobilization in determinations of vital capacity (subject horizontal), ventilation at rest, maximum ventilation capacity, breath holding and the Flack test. It is of interest that although maximum ventilation capacity was unimpaired during immobilization, more subjective effort seemed to be required to achieve the same result as was obtained during the control period. The subjects became red-faced and definitely fatigued after performing the test during the latter part of the immobilization period.

14. *Body weight*: The body weight changes during the various periods of study are given in Table x. The changes were small during

each period. During immobilization two subjects gained weight and two subjects lost weight. All four subjects gained weight in recovery.

15. *X-rays of the skeleton:* X-rays were taken of the spine and long bones at three-week intervals on the first pair of subjects. No detectable change in bone density took place during the experiment.

PSYCHOBIOLOGIC EFFECTS OF IMMOBILIZATION*

The four subjects of this experiment, none of whom had a major psychiatric disorder, were studied to determine the psychobiologic effects of immobilization. Data was collected from psychologic examinations, psychiatric interviews and recordings of the subjects' daily experiences. The list contained sixty-five items relating to physical and mental activity and energy, psychosomatic reactions, mood changes, sleep and sexual activity and reactions to doctors, nurses and visitors.

The data revealed that the reactions to immobilization were markedly variable from subject to subject, both in pattern and degree, and were predominantly expressions of the subjects' dominant personality factors.

A subject's immediate reaction to immobilization was similar to that which he experienced in other situations of stress and danger, each subject according to his own dominant personality traits. Thus, one subject whose personality was marked by feelings of insecurity reacted with predominant anxiety and dependency; another who was aggressive became hostile; a Nisei who had been trained to suppress all outward signs of emotion became placid. These reactions occurred during the two days when the cast was fitted, again during the first forty-eight hours of immobilization and once more during the first few days after the cast had been removed. They

therefore appeared to be reactions to new and potentially dangerous situations.

During the course of the six to seven weeks of immobilization each subject manifested, either overtly or indirectly, signs of anxiety, hostility, increased sexual tension and discomfort. Changes also took place during immobilization in mental activity, physical activity and the sleep pattern. The intensity of all these reactions and changes in behavior varied with the personality of the subject. Anxiety, hostility and sexual tension reached their individual maximums at varying periods in each subject. Complaints of physical discomfort (impaired sleep, stiffness and soreness of muscles) were frequent during the first one to two weeks. Thereafter, the subjects were relatively comfortable and carried on activity, including reading and writing with moderate ease. It is to be noted that the Nisei, in keeping with his personality, made almost no complaints of discomfort. Sleep was improved over what it had been in the control period in the subject who reacted with dependency, was unchanged or slightly impaired in others.

Among the physiologic changes observed, all four subjects had a slight decrease in appetite and a gradually increasing generalized weakness with ease of fatigue on the slightest exertion (such as using the bedpan). In two subjects, there was a very slight tendency toward constipation; the other two subjects, who by personality were accustomed to setting patterns of behavior for themselves, set a routine of using the bedpan every evening. In recovery, the subjects noted mild dizziness for one to two days and unsteadiness of the legs for six to eight days. Stiffness and even soreness of the joints, particularly the knees, which began mildly during the last two to three weeks of immobilization, was evident for three to six weeks in recovery. One subject, who had had an injury to one knee years previously, had soreness of both knees for three to four months.

The inconveniences of the experimental procedure, with the exception of immo-

* From The Department of Medicine (Neurology), Cornell University Medical College. This work was carried out by Drs. Kevic Brodman and Bela Mittelman.

bilization in the cast, were accepted by all subjects with great equanimity; however, any disturbance of the good interpersonal relationship of the subject with the doctors or nurses immediately resulted in a violent reaction similar to what the subject experienced in a situation of stress or danger.

COMMENTS

The data presented in this study now make it possible to evaluate the potential contribution of immobilization *per se* to the variety of metabolic and physiologic changes which have been observed to be associated with trauma and disease states in man.

There have been several reports in the literature describing nitrogen and calcium losses following infectious diseases,^{57,58} fractures and surgical procedures⁵⁸⁻⁶³ and in metabolic disorders.^{64,65} The possibility that disuse atrophy from immobilization *per se* might contribute in any significant degree to these metabolic disturbances has been minimized or overlooked. The conditions under which these patients were carried out did not permit a quantitative evaluation of the effects of disuse atrophy since they were limited to patients with traumatic or infectious disorders.

A comparison of the data obtained in this study with those provided by a study on patients with a fracture permits such an evaluation. The best comparative data are provided by the studies of Howard⁶⁶ since the extent and duration of immobilization was most nearly comparable to the conditions of our experiment. This investigator observed total nitrogen losses following a fracture ranging from 124 to 257 Gm., with an average loss of 190 Gm., during four to five weeks after the fracture in five otherwise healthy, young males. The total nitrogen losses of our four subjects over a similar period of immobilization were, on the average, one-fourth to one-fifth as great. It is evident that immobilization of a healthy person provides a stimulus to increased nitrogen metabolism of an appreciable magnitude. Further comparison of How-

ard's patients with our subjects revealed differences in the tempo at which the increase in nitrogen metabolism occurred. Thus, following fracture the increase in nitrogen excretion occurred more rapidly than in the immobilized, healthy adult. After fracture the nitrogen losses were evident within forty-eight hours and reached maximum values by the sixth day. In the healthy, immobilized subject, no increase in nitrogen excretion was evident before the fifth day and the maximum was not reached until the tenth day. It would appear that immobilization does not contribute to the early outpouring of nitrogen following trauma or operative procedures and has no disadvantageous effects on nitrogen metabolism until after the first five or six days.

As in the fracture cases studied by Howard, there were considerable differences in the nitrogen losses between the individual subjects. The nitrogen losses ranged from 30 to 84 Gm. These variations could not be correlated with differences in body type nor could they be related to differences in the state of nutrition of the subjects since all were in an excellent state of well being and nutrition. We were therefore dealing with different responses of the individual subject of quite another character than the variations described by Munro and Cuthbertson⁶⁷ for rats in which the nitrogen losses after trauma could be regularly related to the previous state of nutrition; rats debilitated by a protein-free diet failed to exhibit the rise in nitrogen excretion following fracture which was regularly observed in rats on an adequate protein intake.

In view of the current trend of thought which would relate the nitrogen disturbances after disease states and trauma to alterations in the quality and quantity of the adrenal cortical steroidal hormones,⁶⁸ it is of interest that in only one of the subjects was there any correlation between nitrogen excretion and the urinary content of 17-ketosteroids. In two subjects in whom urinary glycolytic corticoid excretion was determined as well, no significant differences were observed between the control

and immobilization periods. These subjects exhibited neither the increase in urinary corticoids nor the decrease in 17-ketosteroid excretion required by this concept, with one exception. Subject E. M., who exhibited the maximal loss of nitrogen during immobilization, showed a decrease in 17-ketosteroid excretion from the control values of 11.1 mg. per twenty-four hours to an average value of 8.5 mg. per twenty-four hours during the period of immobilization.

The nitrogen losses may now be considered in relation to concomitant changes in phosphorus, potassium and sulfur metabolism. There was remarkably good agreement from week to week in the ratio between urinary sulfur and nitrogen excretion. The ratio of nitrogen to sulfur was consistently that in which these substances are present in muscle protoplasm. The correlation between nitrogen and phosphorus excretion was less good. In three of the subjects, nitrogen excretion during immobilization was significantly greater than was anticipated from the phosphorus excretion not accounted for by calcium, assuming a ratio of nitrogen to phosphorus of 14.7 to 1. In the fourth subject, a discrepancy of about 30 per cent existed in the opposite direction, i.e., less nitrogen was excreted than expected from the concomitant excretion of phosphorus. There was a poor correlation between nitrogen and potassium metabolism. There was a tendency for potassium to move in the same direction as nitrogen and for the potassium balances to become negative during the period of immobilization; however, the quantitative relationships were not close, and there were wide week to week fluctuations in the potassium excretion. In each of the four subjects, the theoretical nitrogen losses based on potassium excretion exceeded the measured nitrogen losses by 61, 46, 27 and 50 per cent, respectively.

Other metabolic studies have yielded equally divergent results with respect to the relation of nitrogen to phosphorus and potassium metabolism. In Benedict's study of a fasting man,⁶⁹ after an initial diuresis of

potassium and phosphorus, the potassium, phosphorus, sulfur and nitrogen losses occurred in the ratio in which these elements exist in muscle protoplasm. On the other hand, Howard's fracture patients stored potassium while they were losing nitrogen and sulfur.⁶⁶

It is doubtful whether the data relating to nitrogen, phosphorus and sulfur metabolism during immobilization can contribute anything of value to a discussion of the controversial subject of "deposit" protein⁷⁰ versus structural or protoplasmic protein as the source of the nitrogen lost. The studies of Schoenheimer and his associates, which have shown the presence of a dynamic equilibrium between the body proteins, tend to throw doubt on the existence of separate categories of proteins in the living organism. It is of interest that the nitrogen losses of well nourished individuals who had been receiving a more than adequate protein diet were at all times accompanied by losses of sulfur in the approximate ratio in which these elements exist in protoplasm. Were there a separate compartment of labile deposit protein in these subjects, it should be of considerable magnitude in view of their previous diet and should have been readily drawn upon during the period of nitrogen loss. Such a phenomenon would have manifested itself in a significant increase in the nitrogen-sulfur ratio during the immobilization phase. Actually, such increases in the nitrogen-sulfur ratio as were observed during the immobilization period over that of the control were extremely small, of short duration and undoubtedly not significant.

It is unfortunately not possible to make a strict comparison of the total calcium losses of our subjects during immobilization with that exhibited by the group of fracture patients studied by Howard, inasmuch as the calcium intake of the latter group was not kept constant during the period of study. With these reservations in mind, the statement seems reasonably justified that over a corresponding period of time the average total excretion of calcium by the healthy,

immobilized adults was at least one-half that of the fracture group. As with the nitrogen excretion, there was a wide variation between subjects as to the extent of calcium excretion during immobilization, two excreting calcium in amounts equal to those found in fractures. Only a very questionable correlation could be made between calcium excretion and body type, the greatest losses occurring in the two tall and slender subjects.

X-rays of the skeleton failed to show evidence of osteoporosis. This might be anticipated from the magnitude of the calcium loss which was equivalent to 1 to 2 per cent of the total calcium content of the skeleton. It is estimated that at least 10 per cent of the total skeletal calcium must be lost for x-rays to show evidence of decalcification.

The alterations in urinary calcium excretion of immobilized healthy subjects and fracture patients are more strictly comparable since the urinary excretion of calcium is not usually greatly altered by minor alterations in calcium intake. The maximum urinary calcium excretion range of seventeen patients with fracture or osteotomy reported by Howard⁵⁵ was 295 to 670 mg. per day with an average maximum of 510. The average maximum daily urinary excretion of the immobilized group was approximately two-thirds that of the fracture group.

These significant increases in urinary calcium excretion, which were far greater than the increases observed in fecal calcium, are of interest in relation to the problem of urinary tract stone formation. Stone formation of the calcium phosphate variety often presents a major complication during immobilization, particularly of orthopedic patients. Major J. J. Joelson⁷¹ reported that the incidence of nephrolithiasis at Crile General Hospital was 7 per cent in cases of fractured femur and 2 per cent in all orthopedic patients. Flocks⁷² has given the incidence as ranging from 5 to 15 per cent in orthopedic patients requiring extensive immobilization. Others have reported unof-

ficially incidences as high as 25 per cent in patients with spinal cord injury.

All of the changes observed during immobilization in the urinary constituents concerned with calcium phosphate solubility would favor the precipitation of calculi, except for the very slight rise in urinary volume. There was a definite and sustained rise of urinary pH throughout the immobilization period which is unfavorable for calcium phosphate solubility. The rises in urinary calcium and phosphate provided an additional tax on the urine to retain these electrolytes in solution. In the normal individual, a shift in urine toward the alkaline side and an increase in urinary calcium excretion is regularly accompanied by an increase in urinary citric acid.⁵⁶ This latter metabolite, by virtue of its capacity to form a poorly ionized, very soluble calcium-citrate complex, exercises a favorable effect on calcium solubility. The absence of any increase in urinary citric acid during immobilization in the face of a higher pH and a greater content of calcium and phosphorus, deprives the organism of this protective device and favors calcium phosphate precipitation. There is no explanation at present for the failure of urinary citric acid to rise during the hypercalcinuria and increased pH during immobilization.

It is unlikely that this derangement is of clinical significance for short periods of immobilization since, although urinary calcium excretion began to increase promptly after the institution of immobilization, high levels were not reached prior to the third or fourth weeks. The possibility of urinary calculi formation would thus appear to be a hazard only to those patients immobilized for longer periods. Renal colic and hematuria have seldom occurred during recumbency in less than ten weeks.⁷³ However, in the tropics, where urine volumes may become markedly reduced, large amounts of calcium phosphate sand and crystals were found within three to four weeks of immobilization in soldiers in North Africa with fractures and severe flesh wounds.⁷⁴

The alterations in calcium excretion during immobilization were accompanied by slight rises in the level of the serum calcium which ranged from 0.8 to 2.1 mg. per cent. In every instance, the original levels were resumed during the last four weeks of the recovery period although in three instances the maximum values occurred during the first two weeks of the recovery period at which time calcium excretion had just begun to diminish. Alkaline phosphatase blood levels were not obtained. Howard⁵⁵ reported a rise in alkaline phosphatase in only one of seventeen patients in his series; this was in a patient with a fracture caused by a bullet.

The progressive reduction in creatine tolerance during immobilization is attributable to the progressive development of a functional impairment of the capacity to store creatine which involved a fairly considerable mass of muscle. The explanation for the absence of significant changes in creatinuria on those days in which no creatine tolerance tests were carried out would appear to reside in the fact that the creatine in the diet did not exceed the capacity of the normal muscle mass in the unimmobilized portions of the body to retain the creatine. This is an explanation which is consistent with many observations which have shown that in patients with localized muscle defects, such as those which result from poliomyelitis, the presence or absence of creatinuria is dependent upon the proportion of damaged to undamaged muscle. However, the extra load imposed by the ingestion of 1.32 Gm. of creatine given on the test day exceeded the capacity of the muscle mass during the immobilization phase and served to unmask the muscle impairment of the immobilized areas. The validity of the creatine tolerance test as a measure of functional or pathologic muscle damage has been well established for Graves' disease, poliomyelitis and progressive muscular dystrophy. In the present study, it would indicate that a functional impairment in muscle creatine metabolism occurred during immobilization and was reversed

when the subjects were restored to full activity. This impairment in creatine metabolism was accompanied by a significant decrease in muscle mass and muscle strength in the immobilized limbs. The effect of immobilization on creatine tolerance observed in the present study would not appear to modify the interpretation of the test in Graves' disease which does not involve the complete immobilization to which those in our study were subjected.

The altered response of the circulation to the upright position as manifested by dizziness, unsteadiness and the tendency to faint has been experienced by many after even brief illnesses requiring bed rest. The results of the tilt table tests in this experiment indicate that bed rest is at least partially responsible for this type of circulatory deterioration and that evidences of it may be detected within one week of the assumption of the recumbent position.

The experiments in which fainting on the tilt table during immobilization was prevented by wrapping the legs in Ace bandages and was not prevented by wrapping the abdomen, point to the legs as the principal vascular area in which important changes occur.

Some of the factors involved in the mechanism of gravity shock and the attempts at preservation of circulation in the upright position are peripheral arterial vasoconstriction, capillary permeability, venous tone, muscle tonus or intramuscular pressure as well as the total circulating blood volume. Investigation of some of these factors and their possible alteration during bed rest was attempted.

One of the methods employed was measurement of leg circumference during tilting. Small and rapid changes in the size of the legs could be readily detected by the use of the device we have described. Analysis of the changes in leg circumference during and following tilting suggested that during the immobilization phase (as compared with the control period), there occurred both greater increases in extravascular fluid and greater progressive increases in venous en-

gorgement in the tilted position. These changes imply either impaired venous or leg muscle "tone" during immobilization or the participation of both factors. Intramuscular pressures were not measured. However, the observed leg muscle atrophy may be relevant and it may have been responsible for lowered muscle tone and reduced support for the leg veins.

The occurrence of purpuric hemorrhages about the feet and ankles in tilt table tests during immobilization is evidence of increased capillary wall fragility or permeability.

The changes in circulating blood volume brought about by immobilization were small and barely significant. Taylor, Erickson, Henschel and Keys¹² have reported more marked changes in three weeks of bed rest in which their subjects were not immobilized and their dietary intake was reduced; they found an average plasma volume loss of 15.5 per cent and total blood volume loss of 9.3 per cent, approximately twice the change found in our subjects.

Relative to the problem of phlebothrombosis, studies of blood coagulation (Lee-White coagulation time and prothrombin time) carried out on arm vein blood showed no increased tendency to coagulation as a result of immobilization. Indeed, Lee-White coagulation times tended to be slightly longer during the bed rest period. These findings suggest that in young, immobilized individuals, in the absence of disease, anesthesia or analgesics, there is no increased tendency of the blood of the general circulation to undergo coagulation.

It was found that there was an average decline in basal metabolism of 6.9 per cent during the immobilization period. It may be safely assumed that the total energy metabolism of the subjects also declined to an even greater extent. From these considerations alone all subjects might have been expected to gain weight since the dietary intake was constant. On the other hand, there were parallel losses of nitrogen of considerable magnitude equivalent to

calculated losses of muscle protoplasm ranging from 0.95 to 2.67 Kg.

The actual weight changes were small. (Table x.) Two subjects gained and two lost weight during immobilization. C. O. gained 1.6 Kg. (his theoretical muscle protoplasm loss was 0.95 Kg.) and A. S. gained 1.0 Kg. (his theoretical muscle protoplasm loss was 1.44 Kg.). E. M. and S. W., who lost greater amounts of nitrogen (theoretical muscle protoplasm losses, 2.67 Kg. for E. M. and 1.79 Kg. for S. W.), lost 1.2 and 0.7 Kg. in weight, respectively.

These relatively small changes in weight are probably the result of the simultaneous loss of muscle protoplasm and storage of fat or carbohydrate. In three of the four subjects, definite development of fat folds in the abdominal wall was apparent at the end of the immobilization period. Measurements of changes in total body water were not carried out but during immobilization there was no storage of sodium or potassium such as would suggest retention of water.

Although we have demonstrated certain detrimental effects of immobilization, particularly in mineral metabolism and circulation, the effect upon basal metabolism gives support to the opinion that bed rest is beneficial in the treatment of tuberculosis. One of the principal reasons for the advocacy of bed rest therapy in this disease has been the inference that energy production is reduced during bed rest. The 6.9 per cent average decline in basal metabolism during immobilization in this experiment would indicate that there is a small but definite reduction in basal energy production during complete bed rest as well as a lowering of total energy production resulting from decreased activity.

The long period required for the various metabolic and physiologic functions to become stabilized following immobilization was impressive. The recovery of metabolic functions in particular was sluggish. (Tables xi, xii, xiii and xiv.) There was a pronounced retention of nitrogen and phosphorus during recovery which continued for six weeks. Calcium metabolism appeared

TABLE XI
METABOLIC BALANCES, SUBJECT E. M., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No	Nitrogen				Calcium				Phosphorus				Potassium			
	Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance*	Intake*	Output		Balance*
		Urine	Feces			Urine	Feces			Urine	Feces			Urine	Feces	
Control																
III	13 55 11 23	1 01 12 24	+1 31	-0 03 0 856 0 078 0 690 0 768	+0 088	-0 043 1 460 0 820 0 517 1 337	+0 123	-0 205	3 15	2 630 374	3 00	+0 15	3 15	2 630 374	3 00	+0 15
IV	13 55 11 63	0 89 12 52	+1 03	-0 31 0 863 0 094 0 697 0 791	+0 072	-0 059 1 485 0 823 0 517 1 340	+0 145	-0 183	3 15	2 560 334	2 89	+0 26	3 15	2 560 334	2 89	+0 26
V	13 50 11 25	0 88 12 13	+1 47	+0 11 0 849 0 068 0 660 0 728	+0 121	-0 010 1 499 0 781 0 516 1 297	+0 202	-0 126	3 15	2 980 377	3 36	+0 21	3 15	2 980 377	3 36	+0 21
VI	13 50 11 12	0 83 11 95	+1 64	+0 28 0 855 0 069 0 690 0 759	+0 096	-0 035 1 473 0 741 0 497 1 238	+0 235	-0 093	3 15	2 680 356	3 04	+0 11	3 15	2 680 356	3 04	+0 11
VII	13 54 11 11	0 83 11 94	+1 60	+0 24 0 852 0 048 0 650 0 698	+0 154	+0 023 1 506 0 840 0 344 1 184	+0 322	-0 006	3 15	2 690 330	3 02	+0 13	3 15	2 690 330	3 02	+0 13
VIII	13 59 11 36	1 03 12 39	+1 20	-0 16 0 849 0 048 0 793 0 841	+0 008	-0 123 1 499 0 736 0 426 1 162	+0 337	+0 009	3 15	2 960 426	3 39	+0 24	3 15	2 960 426	3 39	+0 24
IX	13 55 11 79	0 76 12 55	+1 00	-0 36 0 853 0 036 0 552 0 586	+0 267	+0 136 1 490 0 774 0 300 1 074	+0 416	+0 088	3 15	2 860 260	3 12	+0 03	3 15	2 860 260	3 12	+0 03
Control Base-line, Average of Last Four Weeks	13 57 11 35	0 86 12 21	+1 36	0 0 0 852 0 050 0 671 0 721	+0 131	0 0 1 492 0 773 0 391 1 164	+0 328	0 0	3 15	2 800 343	3 14	+0 01	3 15	2 800 343	3 14	+0 01
Immobilization																
X	13 55 13 51	0 89 14 40	-0 85	-2 21 0 853 0 085 0 674 0 759	+0 094	-0 037 1 490 0 941 0 464 1 405	+0 085	-0 243	3 15	3 080 360	3 44	-0 29	3 15	3 080 360	3 44	-0 29
XI	13 55 14 62	1 12 15 74	-2 19	-3 55 0 856 0 087 0 817 0 904	+0 048	-0 179 1 491 0 962 0 574 1 536	-0 045	-0 373	3 15	3 120 390	3 51	-0 36	3 15	3 120 390	3 51	-0 36
XII	13 56 13 86	0 91 14 77	-1 21	-2 57 0 852 0 102 0 733 0 835	+0 017	-0 114 1 507 0 915 0 517 1 432	+0 075	-0 253	3 15	3 000 333	3 33	-0 18	3 15	3 000 333	3 33	-0 18
XIII	13 55 12 44	1 01 13 45	+0 10	-1 26 0 852 0 119 0 776 0 895	-0 043	-0 174 1 507 0 850 0 528 1 379	+0 128	-0 200	3 15	3 150 343	3 49	-0 34	3 15	3 150 343	3 49	-0 34
XIV	13 55 12 37	1 10 13 47	+0 08	-1 28 0 853 0 106 0 896 1 002	-0 149	-0 280 1 490 0 859 0 622 1 481	+0 009	-0 319	3 15	3 150 326	3 48	-0 33	3 15	3 150 326	3 48	-0 33
XV	13 55 12 32	0 95 13 27	+0 28	-1 08 0 851 0 110 0 780 0 890	-0 039	-0 170 1 524 0 891 0 537 1 428	+0 096	-0 232	3 15	3 300 323	3 62	-0 47	3 15	3 300 323	3 62	-0 47
Average of Immobilization	13 55 13 19	0 99 14 18	-0 63	-1 99 0 853 0 102 0 779 0 881	-0 028	-0 159 1 501 0 903 0 540 1 443	+0 058	-0 270	3 15	3 130 346	3 48	-0 33	3 15	3 130 346	3 48	-0 33
Recovery																
XVI	13 55 12 04	0 90 12 94	+0 61	-0 75 0 854 0 087 0 743 0 830	+0 024	-0 107 1 514 0 854 0 526 1 380	+0 134	-0 194	3 15	2 860 290	3 15	0 00	3 15	2 860 290	3 15	0 00
XVII	13 55 10 49	0 97 11 46	+2 09	-0 73 0 852 0 064 0 790 0 854	-0 002	-0 133 1 506 0 692 0 526 1 218	+0 288	-0 040	3 15	2 500 323	2 82	+0 33	3 15	2 500 323	2 82	+0 33
XVIII	13 55 9 96	0 99 10 95	+2 60	-1 24 0 852 0 060 0 746 0 806	+0 046	-0 085 1 506 0 694 0 462 1 156	+0 350	+0 022	3 15	2 570 290	2 86	+0 29	3 15	2 570 290	2 86	+0 29
XIX	13 55 9 07	1 17 10 24	+3 31	+1 95 0 852 0 043 0 747 0 790	+0 062	-0 069 1 506 0 667 0 503 1 170	+0 336	+0 008	3 15	2 850 390	3 24	-0 09	3 15	2 850 390	3 24	-0 09

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm daily, these figures are probably accurate within ± 0.10 Gm

TABLE XII
METABOLIC BALANCES, SUBJECT C. O., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen					Calcium					Phosphorus					Potassium								
	Intake	Output			Balance	Variation from Control	Intake	Output			Balance	Variation from Control	Intake*	Output			Balance*	Variation from Control						
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total								
Control	13.80	11.00	1.13	12.13	+1.67	+0.13	0.869	0.109	0.680	0.789	+0.080	-0.050	1.540	0.879	0.409	1.288	+0.252	-0.026	3.76	3.28	0.216	3.50	+0.26	+0.28
III	14.42	11.72	1.20	12.92	+1.50	-0.04	0.919	0.109	0.647	0.756	+0.163	+0.033	1.642	0.948	0.397	1.345	+0.297	+0.019	3.76	3.93	0.204	4.13	-0.37	-0.35
IV	14.42	11.20	1.46	12.66	+1.76	+0.22	0.920	0.105	0.733	0.838	+0.082	-0.048	1.607	0.920	0.451	1.371	+0.236	-0.042	3.76	3.54	0.247	3.79	-0.03	-0.01
V	14.42	11.57	1.25	12.82	+1.60	+0.06	0.920	0.126	0.714	0.840	+0.080	-0.050	1.623	0.939	0.422	1.361	+0.262	-0.016	3.76	3.58	0.195	3.78	-0.02	0.0
VI	14.42	11.68	1.10	12.78	+1.64	+0.10	0.920	0.098	0.583	0.681	+0.239	+0.109	1.623	0.927	0.357	1.284	+0.339	+0.061	3.76	3.63	0.159	3.79	-0.03	-0.01
VII	14.42	11.92	1.31	13.23	+1.17	-0.37	0.920	0.134	0.667	0.801	+0.119	-0.011	1.637	0.946	0.417	1.363	+0.274	-0.004	3.76	3.54	0.204	3.74	+0.02	+0.04
Control Base-line, Average of Last Four Weeks	14.42	11.59	1.28	12.87	+1.54	0.0	0.920	0.116	0.674	0.790	+0.130	0.0	1.623	0.933	0.412	1.345	+0.278	0.0	3.76	3.57	0.201	3.78	-0.02	0.0
Immobilization	14.40	12.42	1.29	13.71	+0.69	-0.85	0.919	0.200	0.754	0.954	-0.035	-0.165	1.642	1.006	0.440	1.446	+0.196	-0.082	3.76	3.45	0.214	3.66	+0.10	+0.12
IX	14.42	12.29	1.21	13.50	+0.92	-0.62	0.921	0.254	0.707	0.961	-0.040	-0.170	1.621	1.024	0.429	1.453	+0.168	-0.110	3.76	3.60	0.216	3.82	-0.06	-0.04
X	14.42	12.57	1.22	13.79	+0.63	-0.91	0.919	0.283	0.704	0.987	-0.068	-0.198	1.656	1.095	0.431	1.526	+0.130	-0.148	3.76	3.92	0.166	4.09	-0.33	-0.31
XI	14.42	11.97	1.25	13.22	+1.20	-0.34	0.920	0.314	0.804	1.118	-0.198	-0.328	1.637	1.070	0.477	1.547	+0.090	-0.188	3.76	3.78	0.166	3.95	-0.19	-0.17
XII	14.42	12.38	1.18	13.56	+0.86	-0.68	0.920	0.319	0.800	1.119	-0.199	-0.329	1.639	1.025	0.462	1.487	+0.152	-0.126	3.76	3.76	0.146	3.91	-0.15	-0.13
XIII	14.42	12.47	1.26	13.73	+0.69	-0.85	0.920	0.335	0.754	1.089	-0.169	-0.299	1.639	1.063	0.444	1.507	+0.132	-0.146	3.76	3.62	0.200	3.82	-0.06	-0.04
XIV	14.42	12.35	1.24	13.59	+0.83	-0.71	0.920	0.284	0.754	1.038	-0.118	-0.248	1.639	1.047	0.447	1.494	+0.145	-0.133	3.76	3.69	0.185	3.88	-0.12	-0.10
Average of Immobilization Recovery	14.42	12.33	1.18	13.51	+0.91	-0.63	0.920	0.279	0.632	0.911	+0.009	-0.121	1.637	1.057	0.409	1.466	+0.171	-0.107	3.76	3.65	0.164	3.81	-0.05	-0.03
XV	14.42	10.38	1.58	11.96	+2.46	+0.92	0.920	0.170	0.688	0.858	+0.062	-0.068	1.639	0.917	0.454	1.371	+0.268	-0.010	3.76	3.54	0.264	3.80	-0.04	-0.02
XVI	14.42	9.45	1.80	11.25	+3.17	+1.63	0.920	0.105	0.787	0.892	+0.028	-0.102	1.639	0.872	0.463	1.335	+0.304	+0.026	3.76	3.21	0.282	3.49	+0.27	+0.29
XVII																								

* Potassium intake and balance figures adjusted for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within ± 0.10 Gm.

TABLE XIII
METABOLIC BALANCES, SUBJECT A. S., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen					Calcium					Phosphorus					Potassium					Sodium									
	Output					Variation from Control Base-line	Output					Variation from Control Base-line	Output					Variation from Control Base-line	Output											
	Intake	Urine	Feces	Total	Balance		Intake	Urine	Feces	Total	Balance		Intake	Urine	Feces	Total	Balance*		Intake*	Urine	Feces	Total	Balance	Variation from Control Base-line						
Control	14.42	11.83	2.03	13.86	+0.56	-0.62	0.920	0.108	0.622	0.730	+0.190	+0.028	1.639	0.961	0.466	1.427	+0.212	-0.033	3.76	3.320	0.520	3.84	+0.08	-0.30	4.00	3.00	0.200	3.20	+0.80	+0.34
I	14.42	11.72	2.03	13.75	+0.67	-0.51	0.920	0.136	0.703	0.839	+0.081	-0.081	1.639	0.985	0.457	1.442	+0.197	-0.048	3.76	3.500	0.523	3.52	+0.24	+0.02	4.00	3.500	0.230	3.73	+0.27	-0.19
II	14.42	12.14	1.82	13.96	+0.46	-0.89	0.920	0.130	0.625	0.755	+0.165	+0.003	1.648	0.964	0.447	1.411	+0.237	-0.008	3.76	2.700	0.510	3.21	+0.55	+0.33	4.00	3.300	0.260	3.56	+0.44	-0.02
III†	14.42	12.31	1.82	14.13	+0.29	+0.69	0.920	0.112	0.664	0.776	+0.144	-0.018	1.623	0.920	0.480	1.400	+0.223	-0.022	3.76	2.970	0.560	3.53	+0.23	+0.01	4.00	3.340	0.203	3.54	+0.46	0.00
IV	14.42	10.73	1.82	12.55	+1.87	+0.20	0.919	0.127	0.614	0.741	+0.178	+0.016	1.656	0.976	0.404	1.380	+0.276	+0.031	3.76	3.380	0.490	3.87	-0.11	-0.33	4.00	3.300	0.223	3.52	+0.48	+0.02
V	14.42	11.32	1.72	13.04	+1.38	0.00	0.920	0.123	0.634	0.757	+0.162	0.00	1.642	0.953	0.444	1.397	+0.245	0.00	3.76	3.020	0.520	3.54	+0.22	0.00	4.00	3.310	0.229	3.54	+0.46	0.00
VI	14.42	11.45	1.79	13.24	+1.18	-0.30	0.920	0.162	0.769	0.931	-0.011	-0.173	1.623	0.966	0.501	1.467	+0.156	-0.089	3.76	3.170	0.551	3.72	+0.04	-0.18	4.00	3.720	0.095	3.82	+0.18	-0.28
Average of Last Three Weeks	14.42	12.80	1.71	14.51	+0.09	-1.27	0.919	0.184	0.596	0.780	+0.139	-0.023	1.656	0.919	0.422	1.441	+0.215	-0.030	3.76	3.310	0.466	3.78	+0.02	-0.24	4.00	3.810	0.111	3.92	+0.08	-0.38
Immobilization	14.42	12.70	1.86	14.56	-0.14	-1.32	0.920	0.206	0.692	0.898	+0.022	-0.140	1.637	0.957	0.460	1.517	+0.120	-0.125	3.76	3.080	0.466	3.55	+0.21	-0.01	4.00	3.670	0.123	3.79	+0.21	-0.25
VII	14.42	11.83	1.92	13.75	+0.67	-0.51	0.919	0.204	0.686	0.890	+0.029	-0.133	1.642	0.995	0.469	1.464	+0.178	-0.067	3.76	3.200	0.476	3.68	+0.08	-0.14	4.00	3.720	0.121	3.84	+0.16	-0.30
VIII	14.42	12.68	1.75	14.43	-0.01	-1.19	0.920	0.240	0.669	0.909	+0.011	-0.151	1.637	0.949	0.470	1.519	+0.118	-0.127	3.76	3.420	0.474	3.89	-0.13	-0.35	4.00	3.800	0.125	3.93	+0.07	-0.39
IX	14.42	12.21	2.22	14.43	-0.01	-1.19	0.921	0.249	0.822	1.071	+0.150	-0.312	1.621	1.029	0.590	1.619	+0.002	-0.243	3.76	3.170	0.569	3.74	+0.02	-0.20	4.00	3.780	0.088	3.87	+0.13	-0.33
X	14.42	12.18	1.75	13.93	+0.49	-0.69	0.921	0.236	0.679	0.915	+0.006	-0.156	1.618	1.034	0.466	1.500	+0.118	-0.127	3.76	3.280	0.419	3.29	+0.47	+0.25	4.00	3.580	0.067	3.65	+0.35	-0.11
Average of Immobilization	14.42	12.27	1.90	14.17	+0.25	-0.93	0.920	0.212	0.702	0.914	+0.006	-0.156	1.633	1.021	0.483	1.504	+0.129	-0.116	3.76	3.170	0.489	3.66	+0.10	-0.12	4.00	3.730	0.104	3.83	+0.17	-0.29
Recovery	14.42	11.87	1.72	13.59	+0.83	-0.35	0.921	0.221	0.664	0.885	+0.036	-0.126	1.618	1.008	0.457	1.465	+0.153	-0.092	3.76	2.950	0.440	3.39	+0.37	+0.15	4.00	3.120	0.121	3.24	+0.76	+0.30
XI	14.42	11.22	1.87	13.09	+1.33	-0.15	0.919	0.203	0.711	0.914	+0.005	-0.157	1.639	0.981	0.493	1.474	+0.165	-0.080	3.76	2.690	0.529	3.22	+0.54	+0.32	4.00	3.340	0.164	3.50	+0.50	+0.01
XII	14.42	10.78	2.01	12.79	+1.63	+0.45	0.919	0.183	0.803	0.986	-0.067	-0.229	1.639	0.869	0.517	1.386	+0.253	-0.008	3.76	2.620	0.554	3.17	+0.59	+0.37	4.00	3.380	0.170	3.55	+0.45	-0.01
XIII	14.42	9.32	1.68	11.00	+3.42	+2.24	0.919	0.143	0.636	0.779	+0.140	-0.022	1.639	0.829	0.409	1.238	+0.401	+0.156	3.76	2.620	0.453	3.07	+0.69	+0.47	4.00	2.870	0.181	3.05	+0.95	+0.48
XIV	14.42	9.69	1.77	11.46	+2.96	+1.78	0.919	0.115	0.653	0.768	+0.151	-0.011	1.656	0.841	0.452	1.293	+0.363	+0.118	3.76	2.330	0.560	2.89	+0.87	+0.65	4.00	2.890	0.170	3.06	+0.94	+0.48
XV	14.42	10.22	2.04	12.26	+2.16	+0.98	0.921	0.115	0.697	0.812	+0.109	-0.053	1.618	0.992	0.487	1.479	+0.139	-0.106	3.76	2.240	0.509	2.75	+1.01	+0.79	4.00	3.160	0.211	3.37	+0.63	+0.17

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm daily, these figures are probably accurate within +0.10 Gm

† Urinary output figures given are for first 3 days of period, during 4th, 5th and 6th days subject was away on leave of absence (death of father), 7th day subject resumed diet and control regimen

TABLE XIV
METABOLIC BALANCES, SUBJECT S. W., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen					Calcium					Phosphorus					Potassium					Sodium									
	Output			Variation from Control Base-line	Intake	Output			Variation from Control Base-line	Intake	Output			Variation from Control Base-line	Intake*	Output			Variation from Control Base-line	Intake	Output			Variation from Control Base-line						
	Urine	Feces	Total			Urine	Feces	Total			Urine	Feces	Total			Urine	Feces	Total			Urine	Feces	Total		Urine	Feces	Total			
Control	14.42	12.84	1.19	14.03	+0.39	-0.21	0.920	0.222	0.629	0.851	+0.069	-0.012	1.639	0.953	0.563	1.516	+0.123	-0.016	3.76	3.00	0.489	3.49	+0.27	+0.15	4.00	3.41	0.026	3.44	+0.56	+0.40
I	14.42	12.48	1.34	13.82	+0.60	0.00	0.920	0.212	0.726	0.938	-0.018	-0.099	1.639	0.995	0.597	1.592	+0.047	-0.122	3.76	3.32	0.463	3.78	-0.02	-0.14	4.00	3.93	0.026	3.96	+0.04	-0.12
II	14.42	12.84	1.20	14.04	+0.38	-0.22	0.920	0.213	0.597	0.810	+0.110	-0.029	1.639	0.989	0.590	1.489	+0.150	-0.019	3.76	3.09	0.432	3.52	+0.24	+0.12	4.00	3.86	0.036	3.90	+0.10	-0.06
III	14.42	13.08	1.19	14.27	+0.15	-0.45	0.920	0.216	0.597	0.813	+0.107	+0.026	1.652	0.955	0.510	1.465	+0.187	+0.018	3.76	3.14	0.437	3.58	+0.18	+0.06	4.00	4.17	0.020	4.19	-0.19	-0.35
IV	14.42	12.68	1.06	13.74	+0.68	+0.08	0.920	0.212	0.626	0.838	+0.082	+0.001	1.623	1.002	0.493	1.495	+0.128	-0.041	3.76	3.33	0.449	3.78	-0.02	-0.14	4.00	3.22	0.028	3.25	+0.75	+0.59
V	14.42	12.10	1.12	13.22	+1.20	+0.60	0.919	0.210	0.683	0.893	+0.026	-0.055	1.656	0.905	0.543	1.448	+0.208	+0.039	3.76	3.20	0.477	3.68	+0.08	-0.04	4.00	3.97	0.034	4.00	0.00	-0.16
VI	14.42	12.68	1.14	13.82	+0.60	0.0	0.920	0.213	0.626	0.839	+0.081	0.0	1.643	0.962	0.512	1.474	+0.169	0.0	3.76	3.19	0.449	3.61	+0.12	0.0	4.00	3.81	0.029	3.84	+0.16	0.0
Control Base-line, Average of Last Four Weeks	14.42	12.93	1.07	14.00	+0.42	-0.18	0.920	0.322	0.593	0.915	+0.005	-0.076	1.624	1.109	0.446	1.555	+0.069	-0.100	3.76	3.56	0.419	3.98	-0.22	-0.34	4.00	3.95	0.008	3.96	+0.04	-0.12
Immobilization	14.42	15.44	1.16	16.60	-2.18	-2.78	0.919	0.486	0.607	1.093	-0.174	-0.255	1.656	1.197	0.483	1.680	-0.024	-0.193	3.76	3.70	0.350	4.05	-0.29	-0.41	4.00	4.10	0.009	4.11	-0.11	-0.27
VII	14.42	15.04	1.31	16.35	-1.93	-2.53	0.920	0.563	0.769	1.332	-0.412	-0.493	1.637	1.249	0.589	1.838	-0.201	-0.370	3.76	3.28	0.464	3.74	+0.02	-0.10	4.00	3.88	0.017	3.90	+0.10	-0.06
VIII	14.43	13.56	1.18	14.74	-0.31	-0.91	0.919	0.523	0.660	1.183	-0.264	-0.345	1.642	1.172	0.513	1.685	-0.043	-0.212	3.76	3.44	0.449	3.89	-0.13	-0.25	4.00	4.12	0.022	4.14	-0.14	-0.30
IX	14.42	13.30	1.22	14.52	-0.10	-0.70	0.920	0.575	0.762	1.339	-0.419	-0.500	1.637	1.151	0.517	1.668	-0.031	-0.200	3.76	3.29	0.456	3.75	+0.01	-0.11	4.00	4.02	0.026	4.05	-0.05	-0.21
X	14.42	12.70	1.32	14.02	+0.40	-0.20	0.921	0.577	0.717	1.292	-0.371	-0.452	1.621	1.151	0.516	1.694	-0.073	-0.242	3.76	3.40	0.440	3.84	-0.08	-0.20	4.00	4.02	0.037	4.06	-0.06	-0.22
XI	14.42	13.04	1.44	14.48	-0.06	-0.66	0.921	0.561	0.822	1.383	-0.462	-0.543	1.618	1.219	0.586	1.805	-0.187	-0.356	3.76	2.98	0.511	3.89	+0.27	+0.15	4.00	3.88	0.035	3.92	+0.08	-0.08
Average of Immobilization	14.42	13.72	1.24	14.96	-0.54	-1.14	0.920	0.515	0.704	1.219	-0.299	-0.380	1.633	1.178	0.525	1.703	-0.070	-0.239	3.76	3.38	0.441	3.82	-0.06	-0.18	4.00	4.00	0.022	4.02	-0.02	-0.18
Recovery	14.42	12.68	1.22	13.90	+0.52	-0.08	0.921	0.488	0.743	1.231	-0.310	-0.391	1.618	1.069	0.553	1.622	-0.004	-0.173	3.76	2.98	0.417	3.40	+0.36	+0.24	4.00	3.60	0.041	3.64	+0.36	+0.20
XIV	14.42	11.47	1.39	12.86	+1.56	+0.96	0.919	0.299	0.829	1.128	-0.209	-0.290	1.639	0.923	0.636	1.559	+0.080	-0.089	3.76	2.82	0.546	3.37	+0.39	+0.27	4.00	3.86	0.023	3.88	+0.12	-0.04
XV	14.42	9.81	1.24	11.24	+3.18	+2.58	0.919	0.200	0.707	0.907	+0.012	-0.069	1.639	0.754	0.521	1.275	+0.364	+0.195	3.76	2.62	0.419	3.04	+0.72	+0.60	4.00	3.82	0.022	3.84	+0.16	0.00
XVI	14.42	9.62	1.23	10.85	+3.57	+2.97	0.919	0.139	0.657	0.796	+0.123	+0.042	1.639	0.816	0.494	1.310	+0.329	+0.160	3.76	2.88	0.412	3.29	+0.47	+0.35	4.00	3.43	0.019	3.45	+0.55	+0.39
XVII	14.42	10.28	1.18	11.46	+2.96	+2.36	0.919	0.118	0.527	0.645	+0.274	+0.193	1.656	0.891	0.456	1.347	+0.309	+0.140	3.76	2.35	0.380	2.73	+1.03	+0.91	4.00	3.64	0.030	3.67	+0.33	+0.17
XVIII	14.42	10.39	1.15	12.14	+2.28	+1.68	0.921	0.151	0.497	0.648	+0.273	+0.192	1.618	0.905	0.474	1.379	+0.239	+0.070	3.76	2.20	0.374	2.57	+1.19	+1.07	4.00	3.44	0.030	3.47	+0.53	+0.37
XIX	14.42	10.39	1.15	12.14	+2.28	+1.68	0.921	0.151	0.497	0.648	+0.273	+0.192	1.618	0.905	0.474	1.379	+0.239	+0.070	3.76	2.20	0.374	2.57	+1.19	+1.07	4.00	3.44	0.030	3.47	+0.53	+0.37

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within ± 0.10 Gm.

to require even longer for readjustment. The highest serum calcium levels occurred during the first and second recovery weeks. The loss of calcium was still occurring three weeks after mobilization. Of the two subjects studied for six weeks after mobilization, one still showed marked calcium retention at the end of that time.

On the other hand, the impairment in creatine metabolism was repaired within three to four weeks and, in general, most of the physiologic functions appeared to be regained within this period. The basal metabolic rate, muscle strength, the reaction of the circulation to the erect position and the blood volume all returned to control levels in three to four weeks. Certain tests required a longer period for recovery. Exercise tolerance required four to six weeks and girth of the extremities five to six weeks; the reclining pulse rate had not yet returned to pre-rest levels after six weeks.

In conclusion, we wish to emphasize that the undesirable effects of immobilization which have been demonstrated are to be anticipated only in very ill patients or in those who are immobilized due to trauma, surgical procedures, poliomyelitis and similar disease conditions. Only a small percentage of hospital patients are immobilized to the same degree as were the subjects in this experiment. From the results of this study there would seem to be little danger to the average patient from unrestricted bed rest for at least the first two to three weeks. The nitrogen losses, although definite, were not marked; changes in calcium metabolism, muscle mass and strength were not pronounced until after the first two to three weeks; an increased tendency to coagulation of the blood of the general circulation was never demonstrated.

However, for the patient rather rigidly immobilized and forced to remain so for several weeks, there appear to be certain hazards. The threat of urinary tract stone formation, the impaired response of the circulation to the upright position, the derangement in creatine metabolism and

loss of muscle mass and strength may become of real concern.

SUMMARY

A study of the effects of immobilization upon various metabolic and physiologic functions of four normal, healthy, young men was carried out on a metabolism ward during control (five to seven weeks), immobilization (six to seven weeks) and recovery (four to six weeks) periods. Throughout the study, dietary intake was kept constant. During the immobilization period the subjects were placed in bi-valved plaster casts extending from the umbilicus to the toes.

1. Nitrogen excretion began to increase on the fifth to sixth day of immobilization and reached its peak during the first half of the second week. Total nitrogen losses ranged from 29.8 to 83.6 Gm., and averaged 53.6 Gm.

2. Both urinary and fecal calcium excretion increased during immobilization, maximum excretion being reached by the fourth to fifth week. Total calcium losses ranged from 9 to 23.9 Gm. The calcium content of the urine was doubled during immobilization. The absence of appreciable increase in urine volume, the slight rise in urinary pH and the failure of urinary citric acid to rise parallel with the increase in calcium would all favor the precipitation of calcium phosphate in the urinary tract. A slight elevation in serum calcium levels occurred at the end of the immobilization period.

3. During immobilization there was an increase in the excretion of phosphorus, total sulfur, sodium and potassium. Total sulfur was excreted in the urine in close correlation from week to week with urinary nitrogen in the ratio in which these elements exist in muscle protoplasm. The changes in phosphorus excretion showed moderately good correlation with the changes in nitrogen and calcium excretion.

4. During recovery there was retention of nitrogen, calcium, phosphorus, sulfur and potassium. The recovery or return to control levels of metabolic functions was slow, retention of nitrogen and phosphorus

continuing for six weeks. Re-stabilization of calcium metabolism appeared to require more than six weeks.

5. Although creatine and creatinine excretion remained fairly constant, there was a definite lowering of creatine tolerance during immobilization. This impairment in creatine metabolism was accompanied by a significant decrease in muscle mass and muscle strength in the immobilized limbs.

6. In only one subject was there a significant lowering of 17-ketosteroid excretion during immobilization; this subject also experienced the largest nitrogen losses.

7. The decline in basal metabolic rate during immobilization averaged 6.9 per cent among the four subjects.

8. Immobilization brought about a deterioration in the mechanisms essential for adequate circulation in the erect position as indicated by an increased tendency to faint in tilt table tests. Experiments indicated that the legs were the principal site of changes responsible for this deterioration and suggested that increased venous engorgement, increased extravascular fluid, capillary fragility and impaired venous or muscle tone play a rôle.

9. Other circulatory changes brought about by immobilization were a decline in total blood volume averaging 5.4 per cent, marked decreases in exercise tolerance as measured by Master and Schneider tests and an increase in the resting pulse rate of 3.8 beats per minute during immobilization, followed by an additional increase of 4.7 beats per minute during the first three weeks of recovery.

10. The recovery or return to control levels of most physiologic functions required three to four weeks; exercise tolerance and leg girth required four to six weeks and the reclining pulse rate more than six weeks.

11. Changes in body weight during immobilization were small, probably as a result of the simultaneous loss of muscle protoplasm and storage of fat or carbohydrate.

12. There were no significant changes due to immobilization in blood coagulation studies, blood circulation time, heart size,

electrocardiograms, resting arterial blood pressure, hematocrits, blood counts, vital capacity, maximum ventilation capacity or breath-holding.

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Experiences in the Management of Subacute Bacterial Endocarditis Treated with Penicillin*

PHILIP A. TUMULTY,† M.D. and A. McGEHEE HARVEY, M.D.
Baltimore, Maryland

NUMEROUS reports have been made in the literature concerning the treatment of subacute bacterial endocarditis with penicillin.¹⁻⁹ It appears that a majority of the patients with this disease can be cured of their infection if adequate dosage of penicillin is given for an adequate period of time. These results are in dramatic contrast to those achieved with any form of therapy hitherto employed. Recovery rate in sulfonamide-treated patients was at best between 2 and 10 per cent,^{3,10} little better than Libman's estimated spontaneous recovery rate of 3 per cent.¹¹ However, there are still many problems in the diagnosis, treatment and practical management of patients with this disease which are not yet fully understood or appreciated. Clinical recognition of bacterial endocarditis is frequently delayed for many months and bacteriologic diagnosis may be very difficult. Complicating factors such as embolic phenomena, cardiac or renal insufficiency, acute rheumatic fever and sensitivity to penicillin may arise during the course of treatment and profoundly affect the result. The constitution of adequate treatment has not been clearly defined and it becomes quite clear upon reviewing reported failures in treatment that many such patients have not been given adequate amounts of penicillin over a sufficient period of time. Present information concerning the progress and ultimate outcome of patients successfully cured of their infection by penicillin is inadequate. As

large statistics obtained under uniform conditions are not yet available, it is hoped that this account of experiences in handling a group of patients with subacute bacterial endocarditis will add something to the present understanding of these problems.

In any consideration of subacute bacterial endocarditis, it is important to point out that one is not dealing with a simple or primary disease process. It is an infection which is superimposed upon an underlying disease or abnormality and the resultant symptoms, physical alterations and clinical course will be the product of both processes. In any given instance, therefore, it may be difficult if not impossible to determine whether some particular clinical feature is due to the subacute bacterial endocarditis alone, or to the underlying process, or to a combination of the two.

CASE MATERIAL

Thirty-five cases constituted the group studied. All were admitted to the wards of the Johns Hopkins Hospital and represent an unselected group of consecutive patients in whom the diagnosis of subacute bacterial endocarditis was established. In addition to the usual supportive measures, penicillin was the only therapy employed. Anticoagulants were not used as there is very little evidence that they are beneficial in the treatment of bacterial endocarditis and there are indications that they may actually be harmful.^{1,12,13}

* From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital, Baltimore, Md.

† Clinical Fellow in Medicine, American College of Physicians, 1946.

TABLE I
PERTINENT DATA OF THE CLINICAL COURSE OF THE PATIENTS WHO DID NOT RECOVER

Case No.	Age	Sex	Race	Duration of Symptoms before Penicillin Treatment	Organism and Sensitivity (units per cc.)	Valve Involved	Daily Penicillin Dosage	Method of Administration	Total Days of Penicillin Treatment	Total Units of Penicillin, Million	Complications	Outcome of Treatment
1	47	M	C	12 days	<i>Streptococcus equinus</i> 0.06	Tricuspid	320,000 × 10 1,200,000 × 10 1,240,000 × 4 2,240,000 × 9 3,600,000 × 28	Intra-muscular Intra-muscular Intra-muscular Intra-muscular Intra-muscular	61	153	Persistent bacteremia during first four courses; sensitivity decreased from 0.06-1.0; moderate degree renal impairment; improved greatly on fifth course of penicillin when suddenly developed abdominal pain and shock; death followed	Autopsy: Heart slightly enlarged; tricuspid valve scarred and covered with vegetations; pulmonary arteries filled with emboli from tricuspid valve; extensive hemorrhagic pancreatitis
2	28	F	W	5 mo.	<i>Alpha streptococcus</i>	Mitral	300,000 × 10 280,000 × 7	Intravenous Intra-muscular	17	5	Improving when suddenly developed upper abdominal mass, became cyanotic and comatose	Autopsy: Heart slightly enlarged; myocardium studded with many small abscesses; mitral valve thickened and covered with vegetations. Aschoff bodies present; splenic infarct; small abscesses in kidneys; ruptured mycotic aneurysm of superior mesenteric artery
3	14	F	C	3 mo.	<i>Streptococcus mitis</i> 0.036	Mitral aortic	320,000 × 14	Intra-muscular	14	4.2	Having satisfactory response when therapy was interrupted for blood cultures; developed progressive cardiac failure, azotemia and jaundice	Autopsy: Heart greatly dilated and hypertrophied; mitral and aortic valves distorted with vegetations. Aschoff bodies present; marked GPC of liver with central necrosis; mycotic aneurysm of cerebral artery
4	11	F	W	5 wk.	<i>Streptococcus mitis</i>	Mitral	600,000	Intra-muscular	26	15.6	End of first week of treatment subarachnoid hemorrhage, followed two weeks later by a second fatal episode	Autopsy: Moderate enlargement of left ventricle; mitral valve distorted, covered with vegetations; atelectasis of left lung with mucus plug; subarachnoid hemorrhage, source not evident
5	17	F	C	9 mo.	Gram-negative anaerobic <i>Coccobacillus</i> ? <i>Bacteroides</i>	Mitral tricuspid	1,200,000	Intra-muscular	9	10.8	Improved, but therapy was halted for minor blood cultures; developed severe progressive cardiac failure, hematuria and azotemia	Autopsy: Vegetations on mitral and tricuspid valves and wall of left auricle with some healing; infarcts in spleen and kidneys
6	23	F	C	1 mo.	<i>Streptococcus fecalis</i> 8.0	Mitral aortic	600,000 × 2 1,200,000 × 6	Intra-muscular	8	9	Persistent bacteremia, acute cardiac failure and death	No autopsy

7	25	F	W	6 mo	Streptococcus fecalis 1 06	Aortic	400,000 X 6 2,400,000 X 6 5,000,000 X 16 5,000,000 X 40	Intra- muscular Intra- muscular Intra- muscular	68	295	Persistent bacteremia with sensitivity decreasing to 6.25 units, recovered from subarachnoid hemorrhage, spleen filled with multiple abscesses which were removed but bacteremia continued	Died at home three months after discharge
8	25	F	W	5 mo	Streptococcus mitis	Mitral	300,000 X 10 240,000 X 30	Intra- muscular Intra- muscular	40	10 3	First course halted because of incipient cardiac failure, bacteremia recurred and continued, developed left hemiplegia and infarcts to spleen and kidneys	Died at home shortly after discharge
9	39	M	W	6 mo	Streptococcus salivarius	Mitral	200,000 X 21 400,000 X 21 400,000 X 12 200,000 X 23	Intra- muscular Intra- muscular Intra- muscular Intra- muscular	77	23	Bacteremia continued, emboli to spleen, kidneys and brain, treatment sporadic because of scarcity of penicillin	Died at home shortly after discharge
10	22	M	W	5 mo	Streptococcus ignavus	Aortic mitral	240,000	Intra- muscular	21	5	Cultures became sterile but there were continued fever, sweats, tachycardia, hematuria and moderate depression of renal function, penicillin halted after splenic and cerebral embolus which developed	Died in coma with progressive cardiac failure
11	57	M	W	2 mo	Streptococcus salivarius	Aortic mitral	200,000	Intra- muscular	8	1 4	Before penicillin started developed acute pulmonary edema and diastolic murmur at aortic area, believed to have ruptured aortic leaflet	Autopsy Heart moderately enlarged, small areas of necrosis in myocardium, fresh vegetations on mitral, aortic valves and aortic surface, 5 X 5 mm rupture of one aortic cusp, marked degree healing of valves, infarcts of spleen and kidneys
12	27	M	W	6 wk	Alpha streptococcus	Aortic mitral	1,200,000 X 21 1,800,000 X 2 2,400,000 X 2 4,800,000 X 4 9,600,000 X 4	Intra- muscular ?	33	84	Cultures became sterile but continued febrile, developed progressive cardiac failure, two episodes of pulmonary embolism, terminal azotemia	Autopsy Heart greatly enlarged, mycotic aneurysm of coronary artery with myocardial infarction, fresh vegetations imposed upon old, healed, calcified endocardium of a bicuspid aortic valve and fresh vegetations also on mitral, infarcts in spleen and kidneys
13	44	M	W	4 mo	Streptococcus salivarius 0 015	Mitral	1,200,000 X 12	Intra- muscular	12	14	Sudden onset of precordial pain with death following	Autopsy Extreme sclerosis of coronary arteries with coronary thrombosis and myocardial infarction, active rheumatic fever, organizing vegetations on mitral valve; splenic infarct

TABLE II
PERTINENT DATA OF THE CLINICAL COURSE OF PATIENTS WHO RECOVERED

Case No.	Age	Sex	Race	Duration of Symptoms before Penicillin Treatment	Organism and Sensitivity (units per cc.)	Valve Involved	Daily Dosage of Penicillin	Method of Administration	Total Days of Penicillin Treatment	Total Units of Penicillin, Million	Complications	Outcome of Treatment	Follow-up Period
14	34	F	W	4 mo.	Alpha streptococcus	i.v. septal defect	250,000	Intravenous	14	3.5	None	Well	36 mo.
15	46	M	W	14 mo.	Bacteroides 1.6	Mitral	600,000 X 6 1,200,000 X 57	Intramuscular	63	73	Moderate depression renal function	Well for five months, then rapidly went into cardiac and renal failure and died; autopsy: rheumatic scarring of mitral and aortic valves, completely healed and calcified erosion of mitral; infarction of right lower lung from mural thrombus right heart; infarction spleen; very extensive interstitial nephritis	5 mo.
16	25	F	W	4 mo.	Alpha streptococcus salivarius	Patent ductus arteriosus	240,000	Intramuscular	30	7.2	Pulmonary embolus lower left lung ten days after treatment started; ductus ligated	Well	24 mo.
17	28	F	C	2 mo.	Alpha streptococcus salivarius 0.045	Mitral	1,200,000	Intramuscular	42	50	None	Well Two months pregnant	7 mo.
18	23	M	W	3 wk.	Gram-negative anaerobic Coccobacillus ? Bacteroides 0.29	Mitral	400,000 X 6 1,200,000 X 14	Intramuscular	20	20	None	Well	18 mo.
19	26	F	W	7 mo.	Alpha streptococcus ignavus	Mitral, aortic	1,200,000 X 35 800,000 X 22	Intramuscular	57	60	None	Well but for mild dyspnea	5 mo.
20	26	F	W	3 mo.	Alpha streptococcus	Mitral	200,000	Intramuscular	21	4.2	Paroxysmal auricular fibrillation	Well until four months after discharge when cultures were again positive for alpha streptococcus. Treated with 7.2 million units of penicillin over twenty-one day period. Well since then	20 mo.
21	44	M	W	5 mo.	Alpha streptococcus mitis 0.0039	Aortic	400,000 X 35 1,200,000 X 21	Intramuscular	56	39	Before treatment started embolus to left superior cerebellar artery; at completion of thirty-five day course of penicillin bacteremia recurred	Well	5 mo.

22	19	F	C	1 mo	Streptococcus salivarius -	Mitral	240,000	Intramuscular	21	5	None	Well	26 mo
23	21	F	W	2 mo	Alpha streptococcus	Mitral	300,000	Intravenous	14	4 2	None	Well	36 mo
24	32	F	W	6 mo	Streptococcus salivarius	Aortic, mitral	300,000 X 14 300,000 X 10 300,000 X 20	Intravenous	44	13 2	Had two recurrences of bacteremia six days after first course and nine days after second, remained sterile after third	Well but for mild dyspnea	28 mo
25	42	F	W	3 mo	Alpha streptococcus	Mitral	300,000 X 14 280,000 X 20	Intravenous Intramuscular	34	10	Had recurrence of bacteremia nine days after first course	Well but for mild dyspnea	29 mo
26	35	M	W	1 mo	Streptococcus mitis 0 056	Mitral	1,200,000	Intramuscular	29	34 8	None	Well	12 mo
27	25	F	C	6 mo	Streptococcus mitis	Mitral	320,000	Intramuscular	13	4 2	None	Well but for moderate dyspnea	32 mo
28	18	F	C	6 mo	Alpha streptococcus	Mitral	300,000 X 9 240,000 X 12	Intravenous Intramuscular	21	5 4	None	Well	30 mo
29	14	M	C	3 mo	Streptococcus equinus 0 0312	Mitral	240,000 X 4 400,000 X 10 1,200,000 X 50	Intramuscular Intramuscular Intramuscular	70	58 6	Persistent recurrence of bacteremia during first two courses of treatment, two weeks after start of third course had a sub-arachnoid hemorrhage	Well but for poor vision of right eye	Inadequate
30	70	M	C	2 mo	Streptococcus salivarius 0 0312	Mitral, aortic	400,000	Intramuscular	23	9 2	None	Well	Died in The State Mental Hospital six months after discharge Cause ?
31	23	F	C	8 mo	Alpha streptococcus	Mitral	1,200,000	Intramuscular	47	56 4	None	Well	5 mo
32	25	F	W	7 mo	Alpha streptococcus mitis 10 00	Mitral, aortic	4,800,000	Intramuscular	42	201 0	Continued minor embolic episodes throughout course	Well but for mild dyspnea on moderately restricted activity	7 mo
33	22	F	W	24 mo	Negative	Patent ductus aortic	1,200,000 X 8 4,800,000 X 35	Intramuscular	43	177	After first course of penicillin fever continued; complete defervescence after increased dosage, patent ductus ligated twenty-fifth day, afterward signs of a more marked, evidence of considerable renal and hepatic damage	Well but for persistent pendant edema	5 mo
34	18	F	W	2 mo	Alpha streptococcus	Mitral	1,200,000 X 11 3,600,000 X 9 7,200,000 X 35	Intramuscular Intramuscular Intramuscular	54	297	Embolus to spleen	Well	4 mo
35	42	M	W	31 mo	Streptococcus salivarius 6 2	Mitral	1,200,000 X 10 12,000,000 X 7 3,500,000 X 15 12,000,000 X 12 18,000,000 X 14 18,000,000 X 42	Intramuscular Intramuscular Penicillin in oil and beeswax Intramuscular Intravenous	100	1,450	Continued evidence of infection until massive dosages employed; on thirty-fifth day embolus to spleen and brachial artery and on eighty-fourth day embolus to spleen. Thighs and buttocks abscessed from intramuscular administration of penicillin	Well on discharge but has developed progressive cardiac enlargement and increasing cardiac failure	3 mo

Symptoms. The symptoms presented by this group of patients are conveniently considered under three headings: (1) those secondary to bacterial infection; (2) those secondary to embolism and (3) those secondary to cardiac disease. In Tables I and II some of the pertinent data of the clinical course of these patients are summarized.

Of the three groups, symptoms arising from infection were by far the most common. The disease almost always manifested itself insidiously so that it was sometimes many months before the patients recognized that their health was seriously affected. In many instances, mild feverishness was the only early symptom. Frank chills did not often accompany the feverishness but sweats and weakness frequently did. An appreciable loss of weight was noted by twelve patients. Joint pains, usually transitory and without marked local reactions, were present in about one-half of the group. In some instances, their presence could be ascribed solely to the bacterial infection while in others the possibility of a concomitant active rheumatic fever had to be considered. Vague musculoskeletal aching was mentioned less often. It is of some interest that the complaints of feverishness, weakness and musculoskeletal aching had led to the diagnosis of grippe in eight patients.

The occurrence of embolism was responsible for the major symptoms of eight patients. Two of these had a cerebral embolus, two developed temporary blindness, two had an embolus to an extremity and the remaining two had emboli to the spleen and kidney respectively. Eight patients noted petechiae in their skin or mucous membranes and a small group told of soreness in the tips of their fingers or toes or of small areas of transitory swelling and tenderness in the soft tissues of the extremities.

Only a small number of patients had complaints indicative of cardiorespiratory difficulty. This confirms the rather important point that patients who develop subacute bacterial endocarditis frequently have only a minimal degree of cardiac disease. Fully two-thirds of our group of patients

had either no history of heart disease or if evidences of heart disease were present they were minimal. Only ten patients had recognized cardiac disease at the time their illness began.

Physical Examination. Weight loss and pallor were the most commonly encountered physical alterations, being present in almost all of the patients. Petechiae were observed in over 50 per cent of the group and there was a similar incidence of splenic enlargement. It is perhaps wise to emphasize the converse of this statement, pointing out that in almost one-half of these patients with proven subacute bacterial endocarditis the spleen was never felt and petechiae were never seen. The liver was believed to be enlarged in seventeen instances. Only one-third of the patients had clubbing of the fingers or toes while tenderness of the toes and fingers was present in but a few individuals. Seven patients had evidences of an acute arthritis. In many of the patients, the heart was thought to show some degree of enlargement although this clinical impression was not always confirmed by teleoroentgenogram. Evidences of frank cardiac failure were observed in only eight of the patients. One patient had auricular fibrillation.

The mitral valve was most frequently involved by the endocardial infection, twenty patients being considered to have only a mitral lesion, while a combined mitral and aortic valvulitis was present in nine instances. Two individuals were found at post-mortem to have vegetations on the tricuspid valve which had not been suspected previously. Two patients had a patent ductus arteriosus and one a patent interventricular septum.

Laboratory Findings. A mild hypochromic anemia was usually present. It was seldom very marked. The white blood count was elevated in only a few instances. In view of the common impression that microscopic hematuria is a frequent and characteristic finding in subacute bacterial endocarditis, it is worth pointing out that fifteen of our patients never developed this finding although

the urine was examined on repeated occasions. The incidence of albuminuria and of white blood cells in the urine paralleled that of hematuria. The results of renal function tests will be discussed at another point.

In all but one instance, an organism was isolated from the blood stream and a positive blood culture was obtained from this individual at another hospital prior to admission and inception of treatment here. The penicillin sensitivity of these organisms was determined in only one-half of the group and ranged from 0.0039 to 10 units.

Great care should be employed in carrying out bacteriologic examinations. Both aerobic and anaerobic cultures should be inoculated. Cultures should be taken at frequent intervals. They should be retained and reviewed for a period of not less than three weeks before they are considered sterile. In several of these cases, the cultures did not show any detectable growth until the second week and in one instance not for twenty-one days. When the diagnosis of subacute bacterial endocarditis seems reasonably certain from a clinical standpoint and yet there is difficulty in obtaining bacteriologic confirmation, mycotic organisms as well as unusual bacteria such as the genus *Bacteroides* should be searched for. There were three cases due to the latter organisms in this group of patients and the isolation of the organisms depended upon long incubation of the cultures anaerobically.

Clinical Course. The majority of our patients were given penicillin by intermittent intramuscular injection usually at intervals of two hours. Although this mode of administration has well recognized disadvantages, in the main it proved to be the most practical and the least distressing to the patient. However, there were instances in which such severe reactions developed at the point of injection that a change to continuous intravenous administration was made. This technic was also used in a few individuals infected with a highly resistant organism for in such instances it was not feasible to achieve adequate penicillin levels

by the intramuscular route. Repeated venous thrombosis was the principal drawback to this method.

The immediate response to penicillin treatment was very striking when the dosage was adequate and when no complications appeared. Blood cultures usually became sterile within one to two days and rarely later than four to five days. Defervescence occurred customarily within three to four days with a concomitant fall in pulse rate. At the same time the patients rapidly developed a sense of well being, the sweats and anorexia steadily vanishing. Although gain in weight and elevation of the hemoglobin and red count were progressive, several weeks were required before normal values were reached. No significant alteration in the white blood count was noted as generally the admission count was normal or a little depressed. In the few instances in which the white blood count was elevated before treatment, a rapid fall to normal took place. In several instances, the sedimentation rate was still elevated at the time therapy was completed despite the fact that all other criteria indicated a successful result. In a few instances, embolic phenomena continued to occur many weeks after the institution of apparently adequate therapy. As isolated occurrences, they were not believed necessarily to be evidences of inadequate treatment.

In the successfully treated group, cardiac function was not appreciably altered during the course of therapy. There was a subsidence of the initial overactivity which was so characteristic upon admission. One patient developed a paroxysm of auricular fibrillation and another several episodes of auricular tachycardia. There were no significant changes noted in the size of the heart. There were no indications of progressive valvular damage except in one instance in which signs of aortic insufficiency appeared during the treatment of a young girl following ligation of an infected patent ductus arteriosus.

Reference has already been made to the fact that a large number of these patients

showed no evidence whatever of renal involvement. In most instances, a mild hematuria and albuminuria were the only evidences of renal implication. Following treatment, these generally disappeared and of the group who made an apparent recovery from endocarditis only two patients manifested depression of renal function while another continued to have a trace of albumin and a few red blood cells in his urinary sediment.

Complications Arising During Therapy. Complications which arose during the course of treatment of these patients can best be grouped and considered under the following headings: (1) those associated with cardiac failure; (2) those associated with embolism; (3) those associated with persistent bacteremia and (4) miscellaneous.

In analyzing the occurrence of these complications, an attempt will be made to relate them to the adequacy or inadequacy of the treatment received. As will be made clear in the discussion, experience in treating this group of patients has altered our concept of "adequate treatment." It has become clear upon review that several of the patients originally considered adequately treated because they were receiving dosages commonly regarded as sufficient (500,000 units daily for three to four weeks)¹⁴ were in fact inadequately treated in the light of additional experience.

Frank cardiac failure occurred in eight individuals. In two instances, therapy was considered adequate while in five it was deemed inadequate. Severe heart failure ending fatally developed in one individual after rupture of an aortic cusp prior to institution of therapy. Of the two patients who developed cardiac failure while receiving adequate treatment, one was found at post mortem examination to have a myocardial infarction secondary to a mycotic aneurysm of one of the coronary arteries while the other was found to have a myocardial infarction secondary to thrombosis of an extremely sclerotic coronary artery. In addition, this latter patient also had rheumatic myocarditis. Three of the pa-

tients receiving inadequate treatment were believed to have rheumatic myocarditis and in two instances this impression was confirmed at postmortem. The other two patients developed cardiac failure during the course of a severe *Streptococcus fecalis* endocarditis which was resistant to treatment. But for these latter cases, it would seem difficult to relate the onset of cardiac failure to inadequate treatment alone and one must conclude, therefore, that in a certain number of patients myocardial insufficiency will occur during the course of subacute bacterial endocarditis regardless of the amount of penicillin employed. This is attributable to the dual nature of the disease process. Although penicillin may be successful in abolishing the bacterial endocarditis, it cannot be expected to alter the underlying cardiac abnormalities which may be responsible for the continued illness or ultimate death of the patient.

Complications Arising from Embolism. The occurrence of emboli to the brain, lungs, kidneys, spleen and peripheral arteries was much more frequent in patients receiving inadequate therapy, eleven of such patients having major embolic episodes as opposed to only three who were undergoing adequate treatment. One patient had a cerebral embolus just before treatment was instituted. Attention has already been drawn to the fact that in a few instances emboli continued to occur many weeks after adequate therapy was begun, one individual having a splenic infarction eighty-four days after commencement of treatment. The suggestion has been made that the institution of penicillin treatment may be responsible for a transient increase in the incidence of embolism as a result of the healing and organization of the affected endocardium. The fact that ten patients gave a history indicative of embolism prior to the reception of any therapy as contrasted to fourteen patients in whom emboli occurred after treatment was started, while far from conclusive, would make it seem improbable that such an impression was valid. The only conclusion which can be drawn from

our experience is that the administration of adequate amounts of penicillin appears to decrease appreciably the occurrence of major embolism.

Persistent Bacteremia. A persistent or recurrent bacteremia was present during the course of treatment of six patients. As would be anticipated, none of these patients was receiving adequate treatment when this occurred. Two of these infections were due to highly resistant strains of *Streptococcus fecalis* and although moderately large dosages of penicillin were used no response was obtained. They were listed as inadequately treated because no attempt was made to employ massive penicillin therapy such as was found to be effective in other highly resistant infections. However, it is quite clear that a more effective antibiotic agent is needed to combat *Streptococcus fecalis* endocarditis. A recurrent bacteremia occurred twice during the course of treatment of one patient and three times in the course of another. In all instances, there was a satisfactory response to penicillin once adequate dosage was established and there was nothing to indicate that subeffective dosages of penicillin had increased significantly the bacterial resistance of the organisms in these cases.

Miscellaneous Complications. Azotemia and reduced renal function were important complications encountered in seven patients. Three of this group were found at autopsy to have renal infarctions and infarctions were also found in a fourth when a nephrectomy was done subsequently to remove a functionless kidney. The kidneys of another patient at autopsy revealed many hyalinized glomeruli, extensive interstitial infiltration and atrophy, and disappearance of tubules and scarring. The sixth in the group, although apparently recovering from the infection, had at the time of discharge a phenolsulfonphthalein excretion of 35 per cent and a urea clearance of 35 per cent with inability to concentrate the urine above 1.018. The last patient died with evidence of progressive renal impairment but the exact nature of his nephritis was not deter-

mined. In none of these instances was there any apparent correlation between the development of renal complications and the adequacy of treatment nor did the length of time the infection had existed untreated seem to be significant.

One patient developed a marked degree of icterus terminally and autopsy disclosed severe chronic passive congestion with marked central necrosis of the liver. Another patient was found at autopsy to have extensive hemorrhagic pancreatitis which had not been suspected during life. The endocardial infection was not thought to have played a part in its causation.

Particular note should be made of a relatively minor but none the less important complication which occurred in two patients. A marked inflammatory reaction with necrosis of the muscles developed at the sites of penicillin injection, associated with moderate elevation of the temperature and general malaise. For a short time this systemic reaction was misinterpreted as evidence of reactivation of the endocarditis.

Results of Treatment. The overall mortality of this group of thirty-five patients with subacute bacterial endocarditis was 37 per cent. However, when nine patients whose treatment was considered to be definitely inadequate were omitted from the series, the mortality was reduced to 20 per cent. Thus, 80 per cent of the patients given adequate therapy recovered from the infection.

It is of interest to compare the apparent causes of death of the adequately and inadequately treated patients. Of the adequately treated group, the pulmonary arteries of one individual were found at autopsy to be filled with emboli originating from vegetations on the tricuspid valve. Another patient had a massive subarachnoid hemorrhage. The remaining two patients had extensive myocardial infarction, in one instance due to occlusion of a sclerotic coronary artery and in the other secondary to a large mycotic aneurysm of one of the coronary vessels. The important observation was made at autopsy that all

four of these patients showed evidence of an active bacterial endocarditis, and this in spite of therapy which had been considered adequate by clinical criteria. Only one of the group showed evidence of active rheumatic myocarditis. The death of six of the nine inadequately treated patients was attributed to cardiac failure. Three of these were thought at autopsy to have acute rheumatic myocarditis and, in addition to this, the myocardium of one individual was studded with multiple small abscesses. Another of the group was found to have a ruptured aortic cusp. Four of these patients had a persistent bacteremia and two of them had multiple emboli to the brain, spleen and kidneys. The last patient in the group died following rupture of an aneurysm of the superior mesenteric artery. Again, it is important to point out that all but one of this group manifested at the time of death an active bacterial endocarditis, either by the presence of persistently positive blood cultures or by the findings at autopsy examination.

In considering the causes of death in the adequately and inadequately treated patients, one is struck by the fact that, but for the instances of rheumatic myocarditis and of myocardial infarction secondary to coronary sclerosis, the deaths are all attributable at least indirectly to a persistence of the bacterial infection. This conclusion is self-evident in those patients who had a continuation of bacteremia and highly probable in those who died as a result of embolism which we have noted is of more frequent occurrence when therapy is inadequate. Thus, the two major causes of death in this group of patients were the character of the underlying cardiac disease and a persistence of the bacterial endocarditis. Several of these patients might have been saved had the antibiotic treatment been more intensive.

Age, sex and race could not be said to have an important influence upon the results of therapy. There was some indication that a long interval of time between onset of symptoms and commencement of treatment was more likely to result in

cardiac insufficiency than was a short interval. However, there were several exceptions, individuals with very long-standing infections having an entirely successful response to treatment. Eight patients had been given one or more courses of inadequate treatment at another hospital prior to admission. The organisms of five of this group were found to be more resistant than average but this apparent decreased sensitivity did not militate against a successful recovery of three of the patients who were given large dosages of penicillin. The other two who received inadequate treatment died. It would seem, therefore, that while one or more courses of ineffective treatment may give rise to more highly resistant strains of organisms, such infections can still be overcome provided an adequate amount of penicillin is given.

There was nothing found in this study to indicate that the particular valve involved by the bacterial endocarditis made a difference in the result. Two of the four adequately treated patients who died were found to have vegetations on the mitral valve alone, one showed involvement of both aortic and mitral valves, and the fourth involvement of the tricuspid valve.

The *Streptococcus fecalis* manifested the highest degree of penicillin resistance, a resistance which became progressively greater as treatment progressed. Both patients infected with this organism died. However, as already pointed out, neither of these patients was given the massive amounts of penicillin which were later found effective in relatively resistant infections.

Thus, in reviewing the results achieved in treating this series of patients, it becomes apparent that success or failure was determined principally by the character of the underlying disease process and of the adequacy of treatment given. While other factors undoubtedly play a part, the major therapeutic concern is that adequate penicillin be given for a sufficient period of time and prior to the development of unalterable cardiac abnormalities.

Follow-up. While it has become apparent that penicillin is a very effective agent in overcoming the infection in most cases of bacterial endocarditis, little is known as yet about the progress of such "cured" patients over a period of years. To what extent does eliminating the infection cure the patient and return him to health? What residuals does a successfully treated subacute bacterial endocarditis leave and to what degree do they interfere with normal cardiac function? Only a post-treatment observation period of long duration can give satisfactory answers. The problem is clearly complicated by the difficulty of estimating how much disability has been produced by the bacterial infection and how much by underlying disease processes. Twenty of the twenty-two patients who were seemingly cured of their infection have been adequately followed since discharge from the hospital. Eight were followed for a period less than six months. During this period four individuals remained entirely well while one complained of mild exertional dyspnea and another has developed progressive cardiac enlargement and symptoms of increasing myocardial failure. One died. He was a forty-six year old white male who was given 73,000,000 units of penicillin over a period of sixty-three days in treatment of a *Bacteroides* infection of the mitral valve with what appeared to be a complete recovery. His course had been complicated by moderate depression of renal function. Following discharge, he got along well on limited activity until five months had elapsed when he rapidly developed signs and symptoms of myocardial and renal insufficiency and died in acute pulmonary edema with azotemia. Post mortem examination revealed scarring of the mitral and aortic valves due to rheumatic fever. There was an entirely healed erosion with calcification of one cusp of the mitral valve with no evidence of an active bacterial endocarditis. In addition, there was an infarction of the right lower lobe of the lung thought secondary to embolism arising from mural thrombi found in the

right side of the heart. Infarcts were also present in the spleen. There was an extensive interstitial nephritis which has already been described. Death was thought due to heart failure and pulmonary infarction. Three patients were followed from six to twelve months, one having mild dyspnea on exertion and the others remaining well. Two individuals were well after a period of eighteen to twenty-four months. Seven patients have been observed from twenty-four to thirty-six months. Four are free of symptoms while three complain of mild exertional dyspnea. Special mention should be made of the only post-treatment recurrence which occurred in the entire series. The patient was a twenty-six year old white female with an undifferentiated alpha-streptococcal infection of the mitral valve who was initially given 4,200,000 units of penicillin over a twenty-one-day period with apparent complete subsidence of infection. However, four months later she again became symptomatic and blood cultures showed growth of an alpha-streptococcus. Alpha-streptococcus was also grown from the socket of an abscessed tooth which was extracted. She was then given 7,600,000 units of penicillin over a twenty-one-day interval with clearing of the infection and she appeared to be well, except for mild exertional dyspnea, when seen twenty months later. Thus, in the twenty patients considered cured of their infection and adequately followed over an interval of three to thirty-six months, there was only one death and one recurrence of infection (or perhaps reinfection), both occurring within six months after completion of therapy. Another patient is showing progressive cardiac enlargement and insufficiency. More than one-half the remainder are entirely well and the rest have evidences of only mild to moderate cardiac insufficiency.

COMMENTS

The importance of early diagnosis now that effective treatment is available is obvious. Although a successful therapeutic result may be achieved despite a long

lapse of time between the onset of the disease and the commencement of treatment, continuation of the infection may result in irreparable damage to the heart or kidneys or allow the occurrence of fatal emboli. The sooner the infection can be brought under control the better the patient's chances for a complete recovery. The diagnosis of subacute bacterial endocarditis is oftentimes a difficult one to make. The classic features of the disease are frequently absent and the presenting manifestations may lead one to suspect a variety of other illnesses. The symptoms arising from the infection have a non-specific character and one may easily misinterpret their true significance unless there is a high index of suspicion of subacute bacterial endocarditis. Embolic occurrences may be distracting and may lead the observer far afield from the true cause of the patient's malady. The evidences of cardiac disease may be minimal. While the physical changes may suggest an endocardial infection, the abnormalities are often not characteristic of the disease and the true nature of the illness may be obscure despite a meticulous physical examination. The diagnosis of subacute bacterial endocarditis can be made at an early date only when the observer appreciates the serious implications of a persistent, unexplained fever in any patient with congenital or valvular heart disease and the proper bacteriologic studies are performed.

The goal of any therapeutic regimen is the cure of the maximum number of patients and not the determination of the smallest amount of an agent which will be effective in the majority of the cases. With this idea in mind, the present concepts of what constitutes adequate treatment of subacute bacterial endocarditis should be reviewed. There can be no doubt of the efficacy of penicillin therapy in the treatment of this disease when it is caused by organisms sensitive to this antibiotic. The chief problem is to determine a program of treatment with penicillin which will be successful in curing the maximum number of patients. It is quite likely that such a

program might entail overtreatment in a few instances but, until means are at hand of singling out such particular cases, the only safe plan to adopt is one which will be successful even against the most resistant infections. Certainly at the present time, there is no entirely satisfactory way of determining before treatment how readily a particular patient can be cured of his infection. Hence, it does not seem extravagant to overtreat some patients in order to assure adequate treatment for all. As has been stated, 80 per cent of the patients who were adequately treated recovered from their infections while inadequate therapy was found to be one of the major causes of death in this series. It cannot be overemphasized that evidence of active bacterial endocarditis was found upon autopsy examination of three of the patients who died while receiving treatment which was regarded as adequate. It is therefore apparent that one should critically appraise present criteria of therapeutic adequacy.

Our experiences led us to adopt 100,000 units given intramuscularly every two hours as the basic treatment schedule. This regimen was amplified by increasing amounts of penicillin as seemed warranted by individual circumstances.

Several factors seemed to be of importance in determining the effective penicillin dosage. Of these, the penicillin sensitivity of the organism was of help in affording an approximation of the penicillin level which would be required to achieve a successful result. However, too much confidence could not be placed in this single factor. As now performed *in vitro*, this test does not accurately reduplicate conditions *in vivo* and the results may be misleading. A few of our patients infected with organisms which were thought to be highly resistant had an excellent response to average therapy and the opposite was also true. Sterilization of blood cultures was also of only limited value for this was usually readily achieved and at times in the face of obvious evidences of continued infection. The concentration of penicillin in the blood required to affect

the organisms present in the vegetations on the heart valve may be considerably greater than that required to render the blood stream free of bacteria. It becomes obvious that reliance cannot be placed on the results of laboratory examination alone as the determinants of penicillin requirements. The best indication of effective therapy proved to be a return of temperature and pulse to normal, gain in weight, absence of sweats, the sense of well being of the patient, the subsidence of embolic phenomena, elevation of the red count and hemoglobin toward normal. Thus, it is only by clinical observation of the patient's general condition that one can satisfactorily determine whether or not an established regimen is adequate.

The sensitivity of the infecting organism having been determined, patients were started upon a therapeutic regimen which was calculated to afford a constant penicillin blood level several times greater than the *in vitro* sensitivity. To just what extent the blood levels should exceed the *in vitro* sensitivity in order to produce maximal therapeutic effectiveness is still an unsettled question. We attempted to maintain a level five times the sensitivity and this appeared to be quite adequate.

Once a patient had been started upon a penicillin regimen determined in this manner, his course was followed closely from day to day and if there was failure to achieve any of the effects mentioned above as indications of therapeutic effectiveness, appropriate daily increments of penicillin dosage were given. This process was continued until a satisfactory response was obtained. In one instance, 20,000,000 units a day were given before the results were deemed satisfactory. In those instances in which there was no determination of *in vitro* bacterial sensitivity, the initial dosage was 1.2 million units a day. Thus, the determination of adequate penicillin dosage in subacute bacterial endocarditis is to a certain extent a matter of clinical trial and error. Chief reliance in gauging the adequacy of any given treatment schedule should be placed upon the general condition

of the patient and not upon such factors as bacterial sensitivity or penicillin blood levels. Such a scheme of dosage, based primarily upon clinical evidence of satisfactory response, will at times entail the administration of massive amounts of penicillin but we are convinced that only by so doing can one save patients who might otherwise be lost through employment of a more conservative dosage plan. The patient in this series who recovered after receiving 1,450,000,000 units of penicillin is a case in point.

When treatment has been started and all clinical evidences of active infection have disappeared, it is extremely difficult to know when a cure has been effected and treatment may be halted. Within certain limits of dosage, the duration of treatment is just as important as the total amount of penicillin given each day. Using a total dose of 5,000,000 units given in courses lasting five, ten and twenty days, Christie² has shown that the percentage of cures was 0, 25 and 50 per cent respectively. On the other hand, when the duration of treatment was uniformly twenty-eight days and the daily dosages were 100,000, 250,000 and 500,000 units, recovery rates were 43, 51, and 61 per cent respectively. Premature discontinuance of treatment may therefore result in failure regardless of the daily quantity of penicillin employed. It is true, as has been mentioned, that a recurrence of bacteremia does not necessarily militate against a successful outcome following an additional course of treatment. The development of a significant increase in bacterial resistance in subacute bacterial endocarditis is apparently unusual.^{1,2} But as we have seen, continuance of infection means that there is much more opportunity for the development of irreparable cardiac and renal damage and for the occurrence of embolism which may be fatal. It is impossible at the present time to set a time limit for the administration of penicillin but the experience of finding evidence of continued bacterial infection in patients thought to have been treated for an adequate period

(four to five weeks) has led us to the belief that therapy should be continued over a period of at least two months after all evidences of active infection have subsided.

Commencement of penicillin treatment at an early date is of obvious importance. Should one, therefore, wait for establishment of a definite diagnosis by positive blood cultures? As has been pointed out, bacterial confirmation may require three or four weeks. Three of the early cases in our series clearly demonstrate what may happen during such a delay. In one patient, rupture of the aortic valve led to acute cardiac failure and death before treatment was begun. In the other two instances, penicillin administration was interrupted to obtain further cultures when those taken before therapy had failed to reveal an organism. The patients developed an exacerbation of the infection with progressive cardiac insufficiency and died.

On the other hand, initiation of treatment when one has no knowledge of the responsible organism and its sensitivity to various antibiotic agents has its disadvantages and dangers. Once the patient has been committed to a course of penicillin therapy, he is due for an experience which is going to be both expensive and unpleasant. Drug sensitization may ensue. Furthermore, the premature use of the drug may obscure the clinical picture so completely that the clinician does not know with what he is dealing. Without bacteriologic confirmation, not only is it more difficult to establish an adequate dosage schedule but one cannot be certain that the most effective antibiotic agent is being employed for there are instances of bacterial endocarditis in which streptomycin is the antibiotic of choice.^{15,16} This consideration will assume greater importance as new antibiotic agents are introduced. The decision of when to start therapy demands careful clinical judgment. The benefits and danger of delay must be balanced one against the other. Certainly a period of delay, during which intensive bacteriologic studies are made, is advantageous provided the general condi-

tion of the patient does not contraindicate it. However, if bacteriologic confirmation is not obtained after a reasonable period of time and if sound clinical opinion arrives at a diagnosis of bacterial endocarditis, treatment should be commenced without further delay with the assurance that the majority of patients with curable endocarditis will respond to a therapeutic regimen as here outlined and the conviction that to delay is to foster the development of irreparable disease.

As a corollary to what has just been said, antibiotic therapy should not be given to patients having congenital or valvular heart disease for the treatment of a bacterial infection such as pneumonia until blood cultures have been obtained. Such individuals may have a latent bacterial endocarditis which might otherwise be obscured by the initiation of antibiotic therapy. This was brought forcibly to our attention in four individuals who developed endocarditis during an episode of pneumococcal meningitis.

During the process of healing of the bacterial lesion on the valve, rupture or fenestration of a leaflet may occur. It also seems reasonable to assume that cardiac overactivity may be a determining factor in the occurrence of embolism. Therefore, during treatment and for at least one month thereafter every effort should be made to reduce the demands on the circulation to a minimum by limiting the activity of the patient. It is of particular importance in endocarditis of the aortic valve when rupture of a partially healed cusp is observed not infrequently at postmortem.

Consideration of adequate prophylaxis against the development of subacute bacterial endocarditis is as important as the proper treatment of the established infection. Attention has often been called to the frequent occurrence of transient bacteremia following dental extraction and the consequent development of bacterial endocarditis is well recognized. Six of the patients in this series had the onset of their infections following extraction of teeth. However, not so well recognized are the potential dangers

of obstetric, gynecologic, urologic or other surgical procedures both major and minor. Two of these patients developed endocarditis after an abortion, one following manipulation of a fractured femur, one after a hemorrhoidectomy and one post partum. Hence, it seems obvious that adequate prophylaxis must be employed when any procedure, major or minor, is undertaken which might result in a transient bacteremia. Such prophylactic treatment must be given even to individuals with minimal evidence of valvular heart disease. Since the organisms producing bacterial endocarditis have a widely varying sensitivity to penicillin, it would seem wise to employ at least 500,000 units of penicillin daily as a prophylactic measure. Even this dosage may be inadequate protection against such organisms as the *Streptococcus fecalis*. The period of administration should be for not less than four days following the procedure.¹²

In addition to antibiotic prophylaxis, attention should be called to the importance of searching for and eliminating all foci which might serve as a reservoir of infection or reinfection. One of these patients had a recurrence several months after what seemed to be a successful course of treatment. An alpha-streptococcus was grown from her blood and also from the socket of an abscessed tooth which was extracted. She has subsequently remained well following a second course of treatment.

Because of the dual nature of subacute bacterial endocarditis, one must anticipate that a certain number of patients will develop cardiac failure, perhaps ending in death, as the result of irreparable damage to endocardium and myocardium even though cured of infection by penicillin. This damage may result either from the infection or the underlying process. In any given instance, it would obviously be difficult to estimate the degree of responsibility for cardiac impairment attributable to the bacterial endocarditis or to the underlying heart disease. There is nothing to indicate that the administration of penicillin precipitates cardiac failure in patients with

subacute bacterial endocarditis through any mechanism such as rapid dissolution of bacterial vegetations before healing has progressed sufficiently. Fiese¹⁷ has shown statistically that treatment with penicillin postpones cardiac failure and reduces significantly its incidence. Approximately 30 per cent of his series of twenty-five treated patients suffered cardiac failure as contrasted with 80 per cent in a group of forty untreated patients followed to autopsy. In our series of patients, about eight died in cardiac failure. We have studied the effect of the cardiac status prior to the onset of bacterial endocarditis upon the ultimate outcome of treatment and also upon the incidence of myocardial insufficiency occurring during the course of the disease. Two individuals with mild cardiac failure prior to the onset of their infection died during the course of treatment from apparent cardiac failure while four patients similarly affected recovered from their infection. Two of this group have remained entirely well while the other two still have evidences of mild cardiac insufficiency. These patients have been followed for periods of four, twenty-six, twenty and thirty-six months respectively. Only one patient had had severe cardiac failure prior to the development of endocarditis and he died during treatment. After the development of bacterial endocarditis seventeen of this series of patients showed evidence of varying degrees of cardiac impairment, manifested either by enlargement of the heart or signs and symptoms of obvious failure. Of these, ten had never previously manifested cardiac insufficiency prior to the development of bacterial endocarditis while six had shown a mild degree and one a severe degree of impairment. When the effect of the development of cardiac impairment after the onset of endocarditis was related to the ultimate outcome of treatment, it was found that all four of the patients who developed severe cardiac failure died while ten who had only a mild degree recovered and three similarly affected died. One-half of the group who recovered have remained apparently well

over a period of observation varying between three and thirty months while the remainder still show a mild degree of cardiac inadequacy. A single patient has shown progressive cardiac enlargement and failure three months after termination of treatment. It would thus seem that a severe degree of cardiac impairment present either before or after the development of bacterial endocarditis carries a very bad prognosis, such patients usually dying of cardiac failure despite the institution of penicillin treatment. On the other hand, patients with only a mild degree of cardiac damage incurred either before or after the onset of bacterial endocarditis generally have a successful outcome of penicillin treatment and during the period of observation have not shown a tendency to develop progressive cardiac failure, with but one exception. This latter point is a most important and encouraging observation. As was to be expected, all the individuals who had cardiac insufficiency before the development of bacterial endocarditis continued to show this disability after the onset of their infections, but cardiac inadequacy of greater or less degree frequently appeared during the course of subacute bacterial endocarditis in individuals who had not been previously so affected. The age of the patient and the type of underlying valvular disease did not seem to have any prognostic significance. There was some indication that a long interval of time between onset of symptoms and commencement of treatment was more likely to result in cardiac insufficiency than was a short interval but the difference was not statistically significant in this small group of patients.

Consequently, it becomes apparent that despite adequate penicillin treatment, failure must be anticipated in a certain number of instances. At times this will be due to cardiac failure. In others, an embolic episode may be responsible or the infection may be caused by bacteria insensitive to available antibiotic agents. The final determinants of success in the penicillin treatment of this disease are not primarily such factors as the

age of the patient, the duration of the disease or the particular valves involved but rather the degree of cardiac damage resulting either from the bacterial infection or an underlying disease process, the critical nature of the embolic episodes and the resistance of the infecting organism. These are the factors which determine ultimate success or failure and it is only through the insurance of adequate penicillin treatment that they can be favorably altered.

SUMMARY

Experiences are related in the management of thirty-five patients with subacute bacterial endocarditis treated solely with penicillin on the wards of the Johns Hopkins Hospital. Attention is called to the difficulty of establishing a clinical diagnosis at an early stage of the disease due to the non-specific or misleading character of the presenting symptoms, the frequent absence of classical physical findings and the prevalence of the infection in individuals with only a minimal degree of cardiac disease. The importance of early diagnosis and institution of treatment is emphasized, as continuation of infection may result in irreparable damage to the heart or kidneys or allow the occurrence of fatal emboli, although in several instances a successful therapeutic result was achieved despite a long lapse of time from the onset of disease until commencement of therapy. It is suggested that any patient with a cardiac murmur and a persistent fever should be suspected of having bacterial endocarditis until careful bacteriologic studies and clinical observations have proved otherwise. The necessity of retaining, both aerobically and anaerobically, all blood cultures for a period of not less than three weeks before they are considered sterile is emphasized as is the importance of searching for unusual organisms such as the genus *Bacteroides*. The course of these patients during treatment is described and the complications encountered are analyzed relative to adequacy or inadequacy of treatment received. The conclusion is reached that the two major causes of death were the

underlying cardiac disease and the persistence of bacterial endocarditis. Hence, the major therapeutic concern is that adequate penicillin be given for an adequate period of time and prior to the development of unalterable cardiac abnormalities. The fact that evidence of active bacterial endocarditis was found upon autopsy examination of three patients who died while receiving treatment commonly regarded as adequate has led to critical appraisal of present criteria of therapeutic adequacy. A plan of therapeutic management is described which is thought to assure adequate therapy for the maximum number of patients. In it the penicillin dosage is based primarily upon clinical evidence of satisfactory response. Such factors as the penicillin sensitivity of bacteria, penicillin blood levels and sterilization of blood cultures have been found to have only limited value. The necessity of continuing treatment for an adequate period of time is discussed and the recommendation is made that 100,000 units of penicillin given intramuscularly every two hours for eight weeks be considered the basic and minimal treatment schedule. The pros and cons of initiating treatment before a bacteriologic diagnosis is completed are stated with the conclusion that a reasonable period of delay is justified provided the condition of the patient does not contraindicate such treatment. It is advised that blood cultures be obtained before antibiotic therapy is given to any patient with valvular or congenital heart disease who has a localized bacterial infection, lest a latent bacterial endocarditis be obscured. The value of prolonged convalescence to allow maximal healing of damaged valves is indicated. Consideration is given to the need for adequate prophylaxis against the development of subacute bacterial endocarditis not only during dental extractions but during any type of procedure which might result in transient bacteremia. The elimination of foci of infection which might serve as a reservoir of infection or reinfection is recommended. In conclusion, the immedi-

ate results of treatment are discussed and the course of surviving patients over a three to thirty-six months' period is described. An evaluation is attempted of the influence upon the ultimate outcome of certain factors, including the presence of cardiac failure before, during and after the onset of bacterial endocarditis. The final determinants of failure or success in the treatment of subacute bacterial endocarditis with penicillin appear to be the degree of cardiac damage resulting either from the bacterial infection or an underlying disease process, the severity of the embolic occurrences and the resistance of the infecting organisms.

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Effect of Penicillin on the Bacteremia Following Dental Extraction^{*}

ROBERT J. GLASER, M.D., ARNOLD DANKNER, M.D., SYDNEY B. MATHES, M.D.
and CARL G. HARFORD, M.D.
St. Louis, Missouri

THE bacteremia which often follows dental extraction is believed to be of importance in the pathogenesis of subacute bacterial endocarditis. This investigation was undertaken in an attempt to evaluate the efficacy of penicillin as a prophylactic agent in preventing such bacteremia.

Horder, in 1908, was probably the first to suggest that the portal of entry for the infecting organisms in subacute bacterial endocarditis might often be the oral cavity.¹ Since then, the rôle of transient bacteremia in the pathogenesis of subacute bacterial endocarditis in patients with rheumatic or congenital heart disease has come to be generally accepted²⁻⁹ and is based upon the following considerations: (1) the only route by which bacteria can reach the endocardium is via the blood stream; (2) transient bacteremia frequently follows dental extraction and (3) the onset of bacterial endocarditis often occurs shortly after the extraction of teeth.

It has been shown conclusively by a number of investigators¹⁰⁻¹⁵ that transient bacteremia often occurs after dental extraction; indeed, bacteremia has been demonstrated after the mere chewing of gum or hard candy and following manipulation of teeth without extraction.¹⁶⁻¹⁹ That bacteremia originates because bacteria at the site of extraction gain access to the blood stream has been clearly demonstrated by the ingenious experiment of Burkett and Burn who painted the gingival tissues surrounding

a tooth about to be removed with a fluid culture of *Serratia marcescens*; the organism was recovered from blood cultures obtained shortly after extraction of teeth.²⁰ In Table I, experimental data bearing on these studies are summarized. In addition, it is of interest to note that transient bacteremia may follow tonsillectomy,²¹⁻²⁶ aural surgical operations,²⁷⁻²⁹ manipulative procedures involving the urinary tract,³⁰⁻³⁶ passive motion of suppurative joints and massage of furuncles.¹⁶ Bacteremia and bacterial endocarditis have been reported also following parturition and instrumentation of the female genital tract.³⁷⁻⁴⁷

Although complete bacteriologic studies were not performed in many of the foregoing investigations, the predominating organism recovered was the alpha hemolytic streptococcus which has been shown to be the most common inhabitant of the oral cavity⁴⁸⁻⁵³ and is frequently associated with apical dental infection.⁵²

The temporal relationship between tooth extraction and the onset of subacute bacterial endocarditis has been noted repeatedly by many clinicians.^{14, 15, 18, 54-63}

Once the significance of the oral cavity as the portal of entry of the infecting organisms in bacterial endocarditis was recognized, attempts at prophylaxis were undertaken. Initially, methods such as cautery and curettage were suggested in an effort to prevent the escape of organisms into the blood stream^{55, 60, 64, 65} but experimental evidence of the efficacy of these methods is

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meager. Curettage has been shown to be ineffective.¹² That oral hygiene is important in decreasing the incidence of bacteremia is attested by numerous studies including the present one.^{10,18,60,64}

writers^{14,60,66-69} and experimental studies were undertaken by several groups of investigators. In a series of twenty-seven patients with "congenital or valvular heart disease" who were given sulfapyridine

TABLE I
EXPERIMENTAL INVESTIGATIONS OF BACTEREMIA FOLLOWING DENTAL PROCEDURES

Investigator	Procedure	Dental Condition	Anesthesia	Time of Blood Cultures in Relation to Procedure	No. of Patients in Series	Positive Blood Cultures Per Cent
Richards ¹⁶ (1932)	Gum massage	Inflamed gums	None	Immediately after	17	18
				One hour after	17	0
O'Kell and Elliott ¹⁰ (1935)	Multiple extraction	Marked pyorrhea	General	Immediately after	40	75
	Multiple extraction	Moderate pyorrhea	General	Immediately after	60	70
	Single extraction	Normal	General	Immediately after	10	10
	Two or more extractions	Normal	General	Immediately after	28	43
Round, Kirkpatrick and Hails ¹⁷ (1937)	Patients chewed hard candy	Five patients with dental absorption; others not stated	None	Immediately after	10	20
Burket and Burn ²⁰ (1937)	Extraction and application of Serratia marcescens to the gums	Not stated	Local	Immediately after	53	23
Palmer and Kempf ¹³ (1939)	One or two extractions	Not stated	Local	Immediately after	82	17
				Ten minutes after	82	1.7
Hopkins ¹¹ (1939)	One or two extractions	Not stated	Not stated	Immediately after	108	16.8
				Ten minutes after	1	100
				Thirty minutes after	17	0
Elliott ¹⁸ (1939)	Rocking of tooth	Marked pyorrhea	Not stated	Not stated	21	86
		Normal	Not stated	Not stated	21	25
Murray and Moosnick ¹⁹ (1941)	Patients chewed paraffin for one-half hour	"Dental disease"	None	Immediately after	336	55
Faillor ¹⁵ (1942)	Extraction; unstated number	Not stated	Local	From immediately to six hours after	20	40

Soon after the introduction of the sulfonamides, their use in the prophylaxis of dental bacteremia was suggested by a number of

before and after extraction, blood cultures taken immediately after extraction were sterile and no patient developed bacterial

endocarditis.⁷⁰ Although in this investigation para-aminobenzoic acid was introduced into the media to inhibit sulfapyridine, the failure to include control observations makes evaluation of the results difficult. In another study⁷¹ of ninety-seven patients

it summarizes these reports. One case of fatal bacterial endocarditis, thought to have followed dental extraction performed under sulfanilamide prophylaxis, has been reported.⁶²

The use of penicillin in the prophylaxis of subacute bacterial endocarditis after dental

TABLE II

EXPERIMENTAL INVESTIGATIONS OF THE EFFECT OF SULFONAMIDE PROPHYLAXIS ON DENTAL BACTEREMIA

Investigator	Procedure	Dental Condition	Anesthesia	Time of Blood Sampling in Relation to Procedure	No. of Patients in Series		Positive Blood Cultures Per Cent	
					Control Group	Sulfonamide Group	Control Group	Sulfonamide Group
Budnitz, Nizel and Berg ⁷⁰ (1942)	Extraction	Not stated	Not stated	Immediately after	..	27	0
				Thirty minutes after	..	27	0
Northrup and Crowley ⁷¹ (1943)	Extraction	Not stated	Local	Immediately after	97	73	12.8	9.6
				Ten minutes after	97	73	0	0
Pressman and Bender ¹² (1944)	Extraction	Normal to marked pyorrhea	Local	Immediately before	30	30	3.3	0
				Immediately after	30	30	83.3	76.7
				Ten minutes after	30	30	33.3	13.3

who did not receive prophylactic sulfonamide therapy, positive blood cultures were obtained in twelve (12.8 per cent) following dental extraction; of seventy-three patients given sulfathiazole, positive blood cultures were obtained after dental extraction in seven (9.6 per cent). The difference in the two series is not statistically significant. It was shown that the prophylactic use of sulfanilamide led to a decrease in the number of positive blood cultures obtained ten minutes after dental extraction but no decrease occurred in the number of positive cultures obtained immediately after extraction.¹² Para-aminobenzoic acid was not used in the media in this particular study. Table

extraction has been advocated by several writers⁷²⁻⁷⁵ but experimental evidence of its value has not yet appeared. The failure of penicillin to prevent bacterial endocarditis after tooth extraction has been reported twice;^{76,77} in one instance,⁷⁶ relatively small doses of the antibiotic were used and in the other⁷⁷ a single injection of 400,000 units of penicillin in oil with beeswax was given prior to extraction. Three other cases of subacute bacterial endocarditis occurring despite the prophylactic use of penicillin have been observed;⁷⁸ in one of these, oral penicillin was being given to prevent streptococcal infection in a child subject to recurrent rheumatic fever.

METHODS

Selection of Patients. The first, or control series, consisted of consecutive, unselected out-patients from either the Dental Surgery Clinic of the Washington University School of Dentistry or the Barnes Hospital Department of Dental Surgery. Subjects for the second, or penicillin, series were in-patients of the Homer G. Phillips Hospital or the Barnes Hospital group; they were seen in consultation by a dental house officer because of the finding of dental disease on physical examination. No patient in either series had received a sulfonamide drug or penicillin for at least one month prior to the observations.

Technic of Blood Cultures. In both series, blood cultures were obtained within one hour prior to extraction before any oral manipulation was done; postoperative cultures were obtained usually within two minutes and always within five minutes of extraction.

Twenty-three cc. of blood were drawn with aseptic precautions and transported immediately to the laboratory in a flask containing 3 cc. of a 4 per cent solution of sodium citrate. A flask containing 100 cc. of beef infusion broth⁵² was inoculated with 10 cc. of blood and for growth under reduced oxygen tension, 10 cc. of blood were placed in a flask of thioglycollate broth.⁷⁹ The latter medium was contained in a Florence flask of 125 cc. capacity in order to decrease the area of the surface in contact with air. In addition, poured plates were made with 1 and 2 cc. amounts of blood added to beef infusion agar. The final pH of all media was 7.6.

In the penicillin series, for both pre- and postextraction cultures, a solution containing 4 units of penicillinase per cc., prepared by diluting dried commercial penicillinase with beef infusion broth, was added to the citrate flasks before the blood was introduced. That this amount of penicillinase was sufficient to cause immediate inactivation of the penicillin in the blood was

determined by preliminary experiments described in a subsequent section.

Cultures were incubated at 37°C. for six days; at that time, the broths were subcultured on blood agar plates and observed for two days; if no growth had appeared, they were discarded. The poured plates were examined at frequent intervals and when colonies were seen they were described according to color and hemolysis. Colonies were then subcultured and the organisms classified morphologically according to Gram-staining characteristics; alpha hemolytic colonies were further characterized in regard to solubility in desoxycholate solution.⁸⁰ Poured plates exhibiting no growth were discarded on the sixth day.

Cultures were considered positive if organisms were recovered from either of the broths or either of the poured plates. In a few instances, organisms were recovered which were considered to be contaminants; these included diphtheroids, *Staphylococcus albus* and *Bacillus subtilis*.

Use of Penicillinase in Blood Cultures. The inactivation of penicillin, carried in the blood drawn from the patient into the culture medium, was considered essential in order that false-negative results might be avoided. Significant disadvantages inherent in the use of takadiastase, clarase and cysteine as penicillin inactivators have been described.⁸¹⁻⁸⁴ Penicillinase, on the other hand, is well adapted to use as an inactivator of penicillin^{83,85-88} and preliminary experiments were performed in order to determine the amount of penicillinase necessary for this purpose under the particular conditions of our blood cultures. Table III shows the results of three experiments which indicate that 4 units of penicillinase per cc. of blood drawn were adequate to inactivate larger amounts of penicillin than would usually be present in the blood with the given dosage. This amount of penicillinase also had no significant inhibiting effect on bacterial growth.

Each test was carried out as follows: The contents of a vial containing 1,000 units of dried commercial penicillinase⁸⁹ were dis-

solved in beef infusion broth and dilutions were distributed in tubes in order to give the amounts of penicillinase shown in the table. Twenty-three cc. of normal human blood were drawn with aseptic precautions and introduced into a flask containing 3 cc. of a 4 per cent sodium citrate solution. A

the citrate before the blood was drawn from the patient in order to start the inactivation of the penicillin carried over in the blood as soon as it was removed from the body. The preliminary tests showed that neither citrate nor human blood inactivated the penicillinase.

TABLE III
DETERMINATION OF THE AMOUNT OF PENICILLINASE NEEDED IN BLOOD CULTURES

Experiment Number	Test Organism	Tube Contents and Results	Tube Number											
			1	2	3	4	5	6	7	8	9	10	11	12
1	Staphylococcus albus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	10	10	10	10	10	10	10	10	10	0	0	0
		Colony count	0	7	30	176	600	TNC*	TNC*	TNC*	0	TNC*	TNC*	TNC*
2	Alpha hemolytic streptococcus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	5	5	5	5	5	5	5	5	5	0	0	0
		Colony count	0	0	2	52	148	183	194	173	0	181	174	186
3	Beta hemolytic streptococcus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	5	5	5	5	5	5	5	5	5	0	0	0
		Colony count	0	0	0	1	4	9	11	9	0	10	9	9

* Too numerous to count.

culture of bacteria in broth was diluted with broth so that suitable numbers of bacteria, as estimated from preliminary tests, could be added to the flask. Two cc. of the resulting blood-citrate-bacteria mixture were added to each tube. Five or ten units of penicillin in 0.5 cc. of broth were added as the last step. After adjusting the volume of each tube to 3 cc. with broth and mixing thoroughly 1 cc. of each mixture was removed immediately for preparation of poured plates. Colony counts were made after incubation at 37°C. for forty-eight hours.

It may be noted in these tests that the penicillin was added last to the mixture in order to avoid any antibacterial action by the penicillin during the time taken in adding penicillinase. In the final blood cultures, the penicillinase was mixed with

Administration of Penicillin. Each of the patients in the penicillin series was given 50,000 units of penicillin intramuscularly every two hours day and night for twenty-four hours before extraction; the total dose was 600,000 units. The last injection was given approximately twenty minutes prior to extraction.

Determination of Penicillin Sensitivity. The sensitivity to penicillin of fourteen of the nineteen strains of organisms recovered in the penicillin series was determined by a modification of the method described by Rammelkamp and Maxon⁹⁰ as employed by Meads *et al.*⁹¹

Observation of Factors Influencing Incidence of Bacteremia. Information concerning factors which might influence the incidence of bacteremia, namely, gum conditions, type

TABLE IV
RESULTS OF BLOOD CULTURES FOLLOWING DENTAL EXTRACTION WITH AND WITHOUT
PROPHYLACTIC PENICILLIN

Control Series*					Penicillin Series†				
Patient	Organisms‡ isolated in				Patient	Organisms‡ isolated in			
	1 cc. Pour Plate	2 cc. Pour Plate	Plain Broth	Thiogly- collate Broth		1 cc. Pour Plate	2 cc. Pour Plate	Plain Broth	Thiogly- collate Broth
1	1				
2	5 A	A	2				
3	3				
4	A	4				
5	A	5				
6	6	2 NH	A	
7	A	A	7	4 NH	NH	NH
8	8	NH	
9	9	NH	
10	7 A	A	10	20 NH	NH	NH
11	7 A	A	11	NH	
12	12				
13	13	A	
14	NH	14	A			
15	2 A	6 A	A	A	15				
16	4 A	2 A	A	A	16				
17	8 A	15 A	A	A	17				
18	A	18	NH	
19	3 A	A	19	NH & A	
20	2 A	20	NH		
21	A	21				
22	A	22				
23	A	23				
24	24	1 NH			
25	1 A	25				
26	2 A	A	A	26				
27	27	A	A
28	1 A	A	A	28				
29	1 A	A	29	1 A	A
30	30				
31	31	32 NH			
32	2 A	A	A	32				
33	33				
34	A	34				
35	A	35				
36	36	A	
37	1 A	A	NH	37	1 A		
38	1 NH	38				
39	1 NH	2 A	NH	NH	39				
40	1 NH	1 A	NH	A	40				

* All pre-extraction cultures in this series were negative.

† Three pre-extraction cultures (No. 3,19,20) were positive for non-hemolytic streptococcus.

‡ A = alpha hemolytic streptococcus.

NH = non-hemolytic streptococcus.

Numbers indicate colony count.

of local anesthetic and number of teeth extracted was obtained for each patient. An arbitrary classification of gum condition was established as follows: (1) normal—no evidence of irritation, inflammation or suppuration; (2) abnormal—evidence of irrita-

extraction both in control patients and in those following prophylactic penicillin. It may be seen that the bacterial content of the blood was never high and that frequently the organisms were recovered from only one of the broths or plates while the other, pre-

TABLE V
EFFECT OF PENICILLIN AND OTHER FACTORS ON THE BACTEREMIA FOLLOWING DENTAL EXTRACTION

Other Factors		Control Series			Penicillin Series		
		No. of Patients	No. of Patients with Bacteremia	Per Cent of Patients with Bacteremia	No. of Patients	No. of Patients with Bacteremia	Per Cent of Patients with Bacteremia
Total No. of Cases		40	27	67.5	40	17	42.5
Condi- tion of gums	Normal	21	12	57.2	11	5	45.4
	Abnormal	19	15	78.9	29	12	41.4
	Gingivitis	8	6	75	13	6	46.2
	Mild to moderate pyorrhea	6	4	66.6	8	1	12.5
	Severe pyorrhea	5	5	100	8	5	62.5
Num- ber of teeth ex- tracted	One	16	10	62.5	26	7	26.9
	Two or more	24	17	70.8	14	10	71.4
Type of local anes- thesia	Infiltration or infiltration and block	24	18	75	13	5	38.4
	Block (conduction) alone	16	9	56.3	27	12	44.4

tion, inflammation or suppuration. Further subdivision of abnormal gums was as follows: (1) gingivitis—irritation or inflammation without suppuration; (2) pyorrhea—definite suppuration, either mild to moderate or severe.

Determination of Statistical Significance. The statistical significance of results was determined by the calculation of chi square from a fourfold table utilizing the correction of Yates for small numbers.⁹²

RESULTS

Table IV presents the results of blood cultures taken immediately following dental

pared from the same blood sample, remained sterile. Nevertheless, the significance of the bacteria isolated is attested by the sterility of pre-extraction blood cultures which were made in every case. In only three instances were pre-extraction cultures positive and in two of these the cultures after removal of the teeth were positive for the same organism. Although the use of prophylactic penicillin reduced by 37 per cent the incidence of bacteremia following extraction and also reduced the number of bacteria as judged by fewer positive isolations from single specimens, it did not completely prevent bacteremia in a number of cases.

Of the twenty-seven positive blood cultures obtained in the control series, twenty-two (81.5 per cent) were due to alpha hemolytic streptococci, two (7.4 per cent) to non-hemolytic streptococci and three (11.1 per cent) to both. In contrast with these results, of the seventeen positive blood cultures in the penicillin series, only five (29.4 per cent) were due to alpha hemolytic streptococci whereas in ten (58.8 per cent) non-hemolytic streptococci were recovered; in two (11.8 per cent) both organisms were present.

The penicillin sensitivity of fourteen of the nineteen strains of organisms recovered from patients who had received the antibiotic prophylactically was determined; the results of these tests did not indicate significant penicillin resistance in any of these fourteen organisms.

In Table v the influence of various factors on the incidence of bacteremia is shown. The use of penicillin did not affect definitely the occurrence of bacteremia in patients with normal gums but in those with evidence of gingival disease there was a significant decrease in the number of positive blood cultures obtained. Examination of the results when the gum condition was more specifically classified, suggests that penicillin was particularly effective when pyorrhea existed but the results in these subgroups are not statistically significant.

Prophylactic penicillin therapy was identified with a significant decrease in the occurrence of bacteremia when only one tooth was removed; when multiple extractions were performed, bacteremia occurred with equal frequency in each series.

The use of penicillin decreased the incidence of bacteremia whether infiltration or block anesthesia was used. In the control series, positive blood cultures occurred less often after block than after infiltration anesthesia.

COMMENTS

It is apparent from the results that penicillin, while effective in reducing the incidence of bacteremia after tooth extraction, did not prevent its occurrence in a

large number of patients. Furthermore, although alpha hemolytic streptococci predominated in the control series and non-hemolytic streptococci in the penicillin series, resistance to penicillin was not demonstrated in the strains of the latter group of organisms. Hence, the failure of penicillin, as used in this study, to prevent bacteremia completely cannot be attributed to resistant bacteria. The explanation for the predominance of one organism in the first series, and another in the second, is not apparent.

The data collected support the contention of other investigators^{10,18} that gum disease predisposes to bacteremia after tooth extraction; under such circumstances penicillin appears to be more effective, presumably by combatting local infection.

In spite of the fact that our results in the control series do not confirm the hypothesis that multiple extractions increase the incidence of bacteremia,^{2,54,55} prophylactic penicillin did decrease the number of positive blood cultures after single extractions. This result suggests that it may be desirable to extract teeth singly when penicillin prophylaxis is indicated.

The influence of the type of anesthesia employed is difficult to evaluate. General anesthesia, which obviates local trauma prior to extraction, has been advocated by several writers;^{2,54,64} others have suggested that local anesthetics containing vasoconstrictors decrease the incidence of bacteremia.^{20,55} No adequate study of this problem has been made and our results do not justify definitive conclusions; in the control series, incidence of bacteremia was significantly lower when conduction anesthesia was used; in the penicillin series, positive blood cultures were equally common with either form of anesthesia. It seems plausible that infiltration anesthesia, because of the trauma incident to its introduction directly at the site of extraction, contributes to the likelihood of bacteremia, especially when gum infection is present.

In a study of bacteremia following dental extractions, care must be exercised with

technical factors such as the media used, prompt inoculation and incubation of the blood cultures, prolonged observation of cultures and adequate identification of organisms. Blood cultures must be obtained almost immediately after extraction, for the number of bacteria in the blood is small (Table II) and decreases rapidly; ten minutes after extraction, positive blood cultures are uncommon.^{10,13,71}

If penicillin is effective as a prophylactic agent in preventing subacute bacterial endocarditis after dental extraction, three possibilities for its mode of action may be considered: (1) complete sterilization of the gums so that bacteremia does not occur, (2) immediate destruction of the organisms in the blood stream so that implantation on the endocardium is prevented or (3) prompt destruction after implantation before clinically detectable involvement occurs. Our observations indicate that complete sterilization of the gums is not achieved with large doses of penicillin for twenty-four hours nor does immediate destruction of the organisms occur in the blood stream since bacteremia was still detected in a considerable number of cases. Nevertheless, the decreased incidence of bacteremia is not without value. Also, the failure to eliminate the bacteremia completely does not necessarily mean that penicillin will not prevent subacute bacterial endocarditis since the antibiotic agent may well inhibit the bacteria after implantation on the endocardium.

Therefore, the following principles are proposed: In patients with rheumatic or congenital heart disease who are to have dental extraction, penicillin should be given in large doses prior to operation; in the presence of gum infection, it should be given for at least twenty-four hours before operation. In all cases, it should be continued for at least two days after extraction or longer, especially if the operative site does not heal. Single extractions are to be preferred to multiple.

The hospitalization of patients for simple dental extraction is not always practical; further information concerning the efficacy

of oral penicillin or of penicillin in oil and beeswax in relation to bacteremia following dental extraction would be of value.

SUMMARY

The administration of large doses of penicillin for twenty-four hours prior to dental extraction caused a significant decrease in incidence of bacteremia following extraction but failed to prevent it in a large number of cases. The agent was particularly effective in decreasing bacteremia after extraction of teeth from infected gums.

The possible *modus operandi* of prophylactic penicillin in preventing subacute bacterial endocarditis is suggested and the recommendation made that this agent be given to all patients with rheumatic and congenital heart disease before and after dental extraction.

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Sulfonamide Therapy of Subacute Bacterial Endocarditis*

JOSEPH SCHEIN,† M.D. and GEORGE BAEHR, M.D.

New York, New York

IN spite of the present availability of newer and more effective antibiotics for the treatment of subacute bacterial endocarditis, a review of experience gained during the pre-penicillin era (1938 to 1943) indicates that the sulfonamide treatment was not without merit. A follow-up study of fourteen patients who were apparently cured by sulfonamides three to eight years ago has been sufficiently rewarding to warrant this report.

ORAL THERAPY

Between 1938, when sulfanilamide was first used for the treatment of subacute bacterial endocarditis, and 1943, when sulfadiazine was replaced by penicillin, ninety-seven patients with the disease were treated with reasonably adequate amounts of one or more of the sulfonamides over a prolonged period. Eighty-one patients received oral therapy, 1.0 to 2.0 Gm. every four hours, for periods ranging from ten days to fourteen weeks.† In this group eight were cured—a recovery rate of 9.8 per cent. In two of the recovered patients hyperthermia was employed in addition to sulfonamide therapy.³

The organisms cultivated from the blood in the eight patients cured by oral medication were *Streptococcus viridans* (five pa-

tients), *Staphylococcus aureus* (one patient) and *Haemophilus influenzae* (two patients).

A variety of sulfonamides was employed in the eighty-one patients treated orally. Of the eight who responded favorably, one received sulfanilamide and fever therapy, one sulfapyridine, three sulfapyridine and sulfanilamide (one of the three also had fever therapy), two had sulfapyridine and sulfathiazole and one had sulfadiazine. The relative cure rate with the different drugs did not seem to be statistically significant. The patients treated with hyperthermia and sulfonamides also were not sufficiently numerous to warrant a conclusion concerning the adjuvant value of fever therapy.

It is of interest to note that there were three patients with *H. influenzae* endocarditis in the series and that two of these three responded favorably to oral sulfonamide therapy. One of the cured patients received sulfadiazine; the other was given sulfapyridine and fever therapy, supplemented subsequently with continuing doses of sulfanilamide.

Among the eighty-one patients who received oral therapy, there were sixty-eight whose infection was due to *Streptococcus viridans*; five of these sixty-eight recovered and were still alive and free of infection two to eight years after completing treatment, a recovery rate for the *Streptococcus viridans* patients of 7 per cent.

It is important to emphasize that in three of the eight patients cured by oral sulfonamide therapy, a *Streptococcus viridans* infection had been engrafted on a congenital heart lesion. In our entire series of ninety-

‡ S. S. Lichtman and W. Bierman reported the results of sulfonamide treatment in fifty-five patients with subacute bacterial endocarditis at The Mount Sinai Hospital previous to 1941. Their statistical observations are not exactly comparable with ours for the years 1938 to 1941 because we have preferred to omit those patients in whom insignificant or only casual doses were employed. For a review up to 1942 see LICHTMAN, S. S., *Ann. Int. Med.*, 19: 787-794, 1943.

* From the Medical Services of The Mount Sinai Hospital, New York, N. Y.

† Welt Fellow in Medicine.

eight patients with subacute bacterial endocarditis who received sulfonamide therapy, there were five instances of congenital heart disease. The fact that three were cured of their infection by oral sulfonamide treatment indicates that bacterial endocarditis

TABLE I

NINETY-SEVEN PATIENTS WITH SUBACUTE BACTERIAL
ENDOCARDITIS TREATED WITH SULFONAMIDES—
1938 TO 1943

<i>Oral therapy</i> —1.0 to 2.0 Gm. every 4 hours for 10 days to 14 weeks	81
Causative Organisms— <i>Streptococcus viridans</i>	68
<i>Streptococcus anhemolytic</i>	6
<i>Streptococcus hemolyticus</i> β	2
<i>Enterococcus</i>	1
<i>Staphylococcus aureus</i>	1
<i>H. influenzae</i>	3
Recovered—follow-up 2 to 8 years	8
<i>Streptococcus viridans</i>	5*
<i>Staphylococcus aureus</i>	1
<i>H. influenzae</i>	2
<i>Massive Intravenous Therapy</i> —30.0 Gm. in 3 hours	16
Causative Organisms— <i>Streptococcus viridans</i>	14
<i>Streptococcus anhemolytic</i>	1
<i>Streptococcus hemolyticus</i> β	1
Recovered—follow-up 2 to 3½ years	6
<i>Streptococcus viridans</i>	6

* This includes three recovered patients (out of a series of five) with congenital heart disease with superimposed *Streptococcus viridans* infection

patients with congenital heart disease have a much better opportunity for recovery with this drug than those in whom the underlying lesion is of the acquired type. Our experience with the treatment of these patients has been so favorable that we believe ligation of a patent ductus arteriosus as performed by Touroff and Vesell⁴ should be deferred until adequate treatment with sulfadiazine or penicillin has been tried.

If the five cardiacs with congenital heart disease are subtracted, our percentage of cures by oral sulfonamide in the remaining sixty-three patients with *Streptococcus viridans* endocarditis falls from 7 to 3.2 per cent. Apparently, the prognosis in regard to oral sulfonamide therapy of subacute bacterial endocarditis is favorable only if the infection is due to *H. influenzae* or other highly susceptible bacteria, or if in patients with *Streptococcus viridans* the infection is based on a congenital heart lesion.

MASSIVE INTRAVENOUS THERAPY

In 1942, Dick⁵ reported the recovery of a patient with *Streptococcus viridans* endocarditis following the intravenous adminis-

tration of 40.0 Gm. of sodium sulfadiazine in 500 cc. of distilled water. An acute renal injury was induced, manifested by hematuria, oliguria and azotemia. As a result of the temporary disturbance in renal function, the concentration of sulfadiazine in the blood attained high levels (89 mg. per cent free and 90 mg. per cent total sulfadiazine) and remained exceedingly high (73 to 23 mg. per cent free, 81 to 47 mg. per cent total sulfadiazine) for eight days. On the fourteenth day intravenous injections were resumed, 5.0 Gm. being administered every two or three days for four injections. The patient's temperature fell to normal within a few hours after the first massive treatment. Blood cultures on the third day and thereafter were sterile.

The massive therapy technic employed by Dick was unquestionably hazardous but by 1942 our own large experience with the prolonged oral administration of sulfonamides had convinced us that about 97 per cent of the patients with *Streptococcus viridans* endocarditis, who did not have a predisposing congenital heart lesion, were doomed to die under the conservative method of oral therapy. We were, therefore, persuaded to employ massive intravenous therapy on the next sixteen patients with subacute bacterial endocarditis due to this and related streptococci.

In each instance 30.0 Gm. of sodium sulfadiazine dissolved in 600 cc. or 1,000 cc. of distilled water was administered by slow, continuous intravenous drip in three hours. This was usually followed by some vomiting. Within twenty-four hours severe oliguria always occurred, the urine became turbid with red cells plus much albumin and the blood urea nitrogen increased to four or six times the normal. In two patients little or no urine was secreted on the first or second day. In six patients the urine became grossly bloody for a day or two. The same intensity of renal injury occurred in ten of the sixteen patients in whom the urine was alkalinized thoroughly before and during the period of treatment by means of bicarbonate of soda administered orally or intravenously.

Sulfadiazine crystals were observed in the urine in moderate amounts in four patients and in minimal amounts in five others. Obstruction of the ureters by sulfadiazine concretions was not encountered in any of the patients, in spite of the huge amounts given intravenously. The low incidence and mildness of crystalluria was probably due to the fact that immediate damage to the renal parenchyma was so severe that very little of the sulfadiazine escaped into the urine during the first week. This hypothesis is supported by the high sulfadiazine blood concentrations observed for seven or ten days after the massive intravenous injection.

The first two patients who received this heroic therapy recovered from the endocardial infection as well as from the renal damage and this encouraged continued trial of the procedure, despite the obvious risks. In fifteen of the sixteen patients treated in this manner the daily volume of urinary excretion returned to normal within seven to fourteen days after the initial intravenous injection of 30.0 Gm. of sodium sulfadiazine; the elevated blood urea nitrogen fell somewhat more slowly before it reached normal levels. Fixation of specific gravity of the urine and low phenolsulphonphthalein excretion rates usually persisted for many weeks or months after the blood urea nitrogen had returned to normal.

Probably in large part because of temporary impermeability of the damaged kidneys, the concentration of sulfadiazine in the blood reached a peak of 40 to 99 mg. per cent within the first twenty-four hours and usually fell slowly during the first week or ten days as renal function was spontaneously reestablished. There seemed to be a rough parallel between the degree and duration of the impairment of renal function and the height of the sulfadiazine level in the blood.

Administration of sulfadiazine was resumed as soon as the concentration in the blood had fallen below 10 mg. per cent. This occurred in various patients from the fourth to the fourteenth day after the initial massive treatment. An attempt was then made to maintain continued high blood

levels, either by one or more intravenous injections of 5.0 Gm. of sodium sulfadiazine (100 cc. of 5 per cent solution) or by the oral administration of 1.0 to 2.0 Gm. of sulfadiazine every four hours "around the clock." Oral sulfadiazine therapy was usually continued in diminishing doses for several months after discharge from the hospital.

One case must be recorded as a treatment fatality. Renal function failed to improve as in the other fifteen patients and the patient died of uremia on the twenty-fourth day. By that day sufficient time had elapsed for complete healing of the tubular damage and the microscopic examination at necropsy no longer revealed the morphologic changes which must have been responsible for the renal insufficiency. A similar fatality after massive intravenous therapy with sulfadiazine was reported by Hull, Bayley and Holoubek.⁶ Two other patients in their series survived but were not cured. Their fourth patient must be discounted, since he was moribund before treatment was initiated and died of the primary disease within sixteen hours.

However, the other side of the picture is impressive. In six of the series of sixteen patients treated in the above manner, blood cultures became sterile after the first massive intravenous injection, the fever and other clinical manifestations of infection subsided and a clinical and bacteriologic cure was apparently effected. All six patients have now been followed for two to three and one-half years; the blood cultures have remained sterile and fever and other clinical indications of bacterial endocarditis have not recurred. The cure rate in this series of sixteen patients treated with massive intravenous injections of sulfadiazine is, therefore, 37.5 per cent. This cure rate is in striking contrast to the results of oral therapy. None of the sixteen had congenital heart disease and none was due to *H. influenzae*. All previously had had rheumatic cardiovascular disease and in all sixteen instances the infecting organism was *Streptococcus viridans* or a closely related streptococcus. They belonged, therefore, to the most unfavorable group in which recovery

after oral therapy could be anticipated in only 3 per cent of the patients.

It is our impression that the blood stream and vegetations were sterilized by the initial intravenous injection of 30 Gm. of sodium sulfadiazine and the extremely high blood levels persisted for a week or more in consequence of renal damage and temporary renal impermeability. Although the continuation of additional intravenous or oral sulfadiazine medication for many weeks or months was probably advantageous in keeping the vegetations sterile until they were completely healed, such prolongation of treatment was not necessarily essential, except perhaps in those patients in whom the initial massive injection failed to produce a sufficiently prolonged high blood level.

CASE REPORTS

CASE I. J. F., was a female, aged fifty-seven years, with *Streptococcus viridans*, 2 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine administered intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three hours) and 5.0 Gm. given intravenously on the seventeenth day. No alkalis were given.

No. of days after injection.	0	1	2	3	4	5	6	8	9
Blood urea nitrogen.....	16				48	61	63	77	82
Blood sulfonamide (mg. per cent free) ...		75	68	67	70	57	64	41	41

No. of days after injection.....	11	15	16	17	18	19	23	29	32
Blood urea nitrogen	88	32	26	31	46	62	79	41	30
Blood sulfonamide (mg. per cent free).	24	0	0	14.5	13.3				

The result was gross hematuria present on the first and second days and oliguria of 20 cc. on the second day. There was a recurrence of oliguria on the seventeenth day following a second intravenous injection. Six blood cultures were sterile after initiation of the therapy. The patient was discharged in the seventh hospital week with a specific gravity of urine fixed at 1.010 and a phenolsulphonphthalein excretion of 40 per cent. The patient was followed for three years. She was found to be afebrile and asymptomatic. The urine was negative for albumin and microscopically; specific gravity

was 1.020; the blood urea nitrogen six months after discharge was 11 mg. per cent. Repeated blood cultures during these years were negative.

CASE II. M. T., was a male, aged thirty-six years, with *Streptococcus viridans*, 36 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three and one-half hours). Beginning on the eighth day, 1.0 Gm. was administered intravenously every four hours for thirty-six hours, then 2.0 Gm. intravenously every four hours for forty hours followed by 2.0 Gm. orally every four hours for fifteen days, 1.5 Gm. every four hours for nine days, 1.0 Gm. every four hours for eight days and thereafter 5.0 Gm. a day (1.0 Gm. every four hours) for thirty-eight days. The patient was alkalinized.

No. of days after injection.....	0	1	2	3	5	8	10
Blood urea nitrogen....	13	12	16	43	23	32	15
Blood sulfonamide (mg. per cent free).....		67	67	40	19	14	34

No. of days after injection . . .	12	14	18	26	35	40
Blood urea nitrogen		8	9	8	10	13
Blood sulfonamide (mg. per cent free)	23	38	32	28	24	18

There was pain in the flanks, nausea, frequent vomiting and singultus for three days after the initial injection. In the urine there was albumin, faint trace to 1 plus, many red blood cells and crystals only on the first day; rare red cells and crystals were present intermittently thereafter. There was oliguria on the first day of 300 cc. Thereafter the urinary output gradually increased to normal by the fifth day. The treatment was discontinued after two and one-half months because of back pain, hematuria and crystalluria in spite of alkalinization. The temperature was normal after the second day, except for an occasional slight rise during intravenous treatment. The first negative blood culture appeared on the fourth day. Thereafter the weekly blood cultures were sterile. The patient was discharged after the seventh week of therapy, with normal blood urea nitrogen but a specific gravity fixed at 1.016. The patient was followed for three and one-half years. He was found to be afebrile and asymptomatic. The blood cultures were sterile. There was no impairment in the urinary concentration and the phenolsulphonphthalein excretion was normal.

CASE III. D. G., was a male, aged twenty-seven years, with *Streptococcus viridans*, 21

colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three hours); 1.0 Gm. administered intravenously every four hours from the fourth to the thirteenth day. Thereafter 1.5 Gm. was given orally every four hours for five days, 2.0 Gm. orally every four hours for twelve days and 1.0 Gm. orally every four hours for ten days.

No. of days after injection.....	1	2	3	5	8	10	16	20	27	36
Blood urea nitrogen....	11	20	23	15	22	18		15		15
Blood sulfonamide (mg. per cent free)...	30	24	18	20	15	48	5	9	8	5

The result was gross hematuria present on the first day, then microscopic for seven days. Moderate oliguria was present only on the first day; thereafter the output of urine was normal. The patient had severe abdominal pain and vomiting the first four days. Many crystals were present in the urine on the seventh day, and it was acid despite alkaline therapy. Fixation of specific gravity below 1.010 was persistent; on discharge the value was 1.012. The temperature fell to normal on the second day, then there was a moderate fever for three days ascribed to phlebitis. After this the temperature was normal continuously. The blood culture was negative on the ninth day. Thereafter repeated blood cultures were sterile. The patient was followed for three years. He was found to be afebrile and asymptomatic, except that he has recently begun to suffer from paroxysmal nocturnal dyspnea. The blood cultures have been sterile and the urine negative, with normal concentrations.

CASE IV. M. S., was a male, aged thirty-four years, with *Streptococcus viridans*, 24 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). Thereafter 2.0 Gm. was given orally every four hours for twenty-eight days, 1.5 Gm. every four hours for four days, 1.0 Gm. every four hours for ten days, and 1.0 Gm. twice a day for forty-five days. No alkalis were given.

No. of days after injection.....	1	2	3	4	5	8	10	13	21	34	39
Blood urea nitrogen....		31	39	55	61	41	33	22	12	16	11
Blood sul- fonamide (mg. per cent free).....	65	41	42	29	44.5	44	31	22	21	19	10.5

The result was gross hematuria present on the second day; later, only occasional red cells were seen in the urine microscopically. There was no decrease in the output of urine. The specific gravity was fixed below 1.010 for fifteen days, then it was below 1.018 until the patient's discharge. Moderate numbers of sulfa crystals appeared in the urine only on the second day. The temperature was normal after the twelfth day. The blood culture was negative on the eighth day. Thereafter repeated blood cultures were sterile. The patient was followed for two and one-half years. He was found to be afebrile and asymptomatic; the blood cultures were sterile and the urine was negative.

CASE V. S. Z., was a female, aged thirty-three years, with *Streptococcus viridans*, innumerable colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). Four days later 1.0 Gm. was given orally every four hours for ten days, 2.0 Gm. orally every four hours for seventy days and 1.0 Gm. every four hours for five months. The patient was alkalinized.

No. of days after injection.....	0	1	2	3	9	11	13	24	30
Blood urea nitrogen....	12	39	25	30	22	15	18	10	5
Blood sulfonamide (mg. per cent free).....		86	40	36	22	14	6.5	29	19

The result was that the patient tolerated the massive dose well; only mild nausea and vomiting occurred. There was no oliguria. The volume of urine was between 1,500 and 2,000 cc. daily. The urine was usually alkaline; no sulfa crystals were present. There was no fever after the second day. The blood cultures were repeatedly sterile after the fifth day. One embolic lesion (finger) appeared ten days after the massive initial dose. Specific gravity of the urine was 1.022. The patient was discharged after eight weeks of treatment and was followed for two and one-half years. Ten days after discharge she was readmitted because of virus pneumonia from which she convalesced uneventfully. During this period of hospitalization the blood cultures were negative and the blood sulfonamide level varied between 17 and 22 mg. per cent. The patient is completely well two and one-half years later. The blood cultures have been sterile and the

urine negative. No signs of reinfection have been seen.

CASE VI. H. H., was a male, aged thirty-one years, with *Streptococcus viridans*, 3 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). On the fifth day he received 2.0 Gm. intravenously and on the sixth day 2.0 Gm. intravenously twice a day. After the ninth day he took 2.0 Gm. orally every four hours and 2.0 Gm. of sodium bicarbonate three times a day for two weeks; thereafter 1.5 Gm. orally every four hours for three weeks, 1.0 Gm. orally every six hours for two months and 0.5 Gm. every six hours for five months.

No. of days after injection.....	1	2	3	4	6	7	8
Blood urea nitrogen....	13	14	52	54	70	76	85
Blood sulfonamide (mg. per cent free).....	43	38	50	42	28	28	11

No. of days after injection.....	12	13	14	15	16	22	26
Blood urea nitrogen	31	54	49	34	25	14	13
Blood sulfonamide (mg. per cent free).	12.5	18	20	19	21	15	11.6

Before admission to the hospital this patient had received small doses of sulfadiazine (1.0 to 4.0 Gm. daily) by mouth for two and one-half months without any influence on the disease. Blood cultures after admission were repeatedly positive, 2 to 4 colonies per cc. After massive therapy he had nausea and vomiting, oliguria, albuminuria and microscopic hematuria. During the first twenty-four hours the urine output declined to 29 cc.; no urine was passed on the second day; on the third day the urine output was 300 cc. and on the fourth day it was again normal (2,000 cc.). The specific gravity of the urine continued to be fixed up to the time of discharge. A week after massive therapy only a few red cells were seen in the urine microscopically and only a few sulfa crystals and casts. The temperature became normal on the seventh day. He was discharged in the fifth week of treatment with a normal temperature, normal sedimentation rate and apparently well, except for a fixation of the urinary specific gravity. Repeated blood cultures after the seventh day following massive intravenous treatment were all sterile. The patient was followed for two and one-half years. He has been afebrile and asymptomatic; there have been no signs of in-

fection and the blood cultures have been sterile and the urine negative.

CONCLUSIONS

1. In the pre-penicillin era (before 1943), oral sulfonamide therapy of patients with subacute bacterial endocarditis, administered in the manner described, resulted in the cure of eight of eighty-one patients, or an overall cure rate of 9.8 per cent. If patients with *H. influenzae* endocarditis and those with congenital heart disease are excluded, the percentage of cures with a three to eight year follow up is reduced to 3.2 per cent.

2. Two of three patients with *H. influenzae* endocarditis were cured by oral sulfonamide therapy. This demonstrates the value of sulfonamides as an alternative to streptomycin in *H. influenzae* infections.

3. Three of five patients with congenital heart disease were cured of *Streptococcus viridans* endocarditis by oral sulfonamide therapy without ligation of the ductus arteriosus.

4. In addition to the patients with *H. influenzae* and congenital heart disease, three other patients with subacute bacterial endocarditis were cured by oral therapy; in two, the infecting organism was *Streptococcus viridans* and in the third it was *Staphylococcus aureus*.

5. Massive intravenous sodium sulfadiazine therapy resulted in the cure of six of sixteen patients with subacute bacterial endocarditis caused by *Streptococcus viridans*. Patients with congenital heart disease were excluded from this series. The six patients have been followed clinically and bacteriologically for two to three and one-half years. The cure rate after massive intravenous therapy is, therefore, 37.5 per cent.

6. Massive intravenous sodium sulfadiazine therapy is attended by a high treatment fatality risk (over 6 per cent). In view of the risk, its use is warranted only in those patients with subacute bacterial endocarditis caused by strains of *Streptococcus viri-*

dans which prove to be resistant to penicillin and streptomycin.

7. In patients with congenital heart disease (not patent ductus arteriosus) and superimposed infection with an organism resistant to penicillin and streptomycin, oral sulfonamide therapy should be employed first; massive intravenous therapy is warranted only after adequate oral therapy has been attempted.

8. If the congenital lesion is a patent ductus arteriosus, ligation is an alternative primary method of therapy; if tying off the ductus is deferred and oral sulfonamide therapy proves successful, the ductus should nevertheless be ligated after recovery from the infection.

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Use of Radioactive Sodium As a Guide to the Efficacy of Drugs Used in Treatment of Diseases of the Peripheral Vascular System*

Preliminary Report

ISIDOR MUFSON, M.D., EDITH H. QUIMBY, SC.D. and BEVERLY C. SMITH, M.D.

New York, New York

OBJECTIVES sought in the treatment of peripheral vascular diseases are the reopening of completely or partially closed blood vessels and the development of an adequate circulation. The vasodilator drugs, papaverine hydrochloride and histamine, have frequently been reported useful in obtaining such results. These drugs may produce transient or prolonged effects. The blanched skin may become flushed and its surface temperature increased. However, at times the same dose seems to be ineffective because there are no such physical changes. Another form of therapy, used especially in thrombo-angiitis obliterans, is the intravenous administration of hypertonic (5 per cent) solution of sodium chloride. This is thought to produce a transitory hydremia. The basis for its usage is essentially empirical. There is no visual or otherwise apparent effect. If one could be assured of pharmacological activity or clinical improvement from these measures, their continued use in chronic peripheral vascular diseases could be undertaken with greater confidence.

Increasing the diameter of a capillary causes an increase in the permeability of its endothelium^{8,9} while a decrease in the diameter reduces the permeability.^{6,8,12}

Therefore, with dilatation of the capillary, crystalloids and fluid should move more rapidly into the pericapillary space.⁸⁻¹⁰ Rate and direction of movement of fluid are dependent upon the relationship between the blood pressure of the capillary, the osmotic pressure of the blood in the capillary and the degree of permeability of the capillary wall.⁷⁻¹⁰ The crystalloids pass through the pericapillary space at a rate specific for each ion to reach an equilibrium on both sides of the semipermeable endothelium according to the Gibbs-Donan formula.⁵

One of the profound disturbances in obliterative diseases lies in the inability of the capillaries to take care of the nutrition of the tissues they permeate. An increase in the rate of transport across the endothelium of such capillaries would mean increased nutrition of the tissues thus supplied. It is therefore reasonable to assume that any method, to be of value in the treatment of peripheral vascular disease, should increase diffusion through the semipermeable membranes of the capillary in addition to enhancing the supply of blood. Such changes in the blood supply or the rate of diffusion can be measured with the aid of the radioactive isotope of sodium according

* From the Departments of Medicine, Radiology and Surgery of the College of Physicians and Surgeons, Columbia University, New York, N. Y.

to the method of Smith and Quimby.¹⁵ They introduce this material into the circulation by intravenous injection and with a Geiger counter note its accumulation in the extravascular fluid in an extremity. This accumulation is dependent upon the patency of the minute vessels, the vascularity of the area and the permeability of the capillary endothelium. An acceleration in rate should therefore be indicative of dilatation of the minute vessels and an increase in available semipermeable membrane.

Davson and Danielli,⁵ in their monograph on the permeability of natural membranes, stated that the use of radioactive isotopes should provide an accurate and rapid method for studying permeability. In accordance with their ideas change in the rate of diffusion of radioactive sodium should be dependable as an indicator of comparable variation in the caliber and permeability of the minute vessel system of the extremities and should also afford a valuable method for the study of the peripheral circulation. Experience with the venous occlusion plethysmograph, skin temperature thermocouples, oscillometer and capillary microscope has shown that they are of great help in studying the peripheral circulation but that they have definite limitations. The greatest difficulty lies in actually getting close to the blood vessels in man. By the use of radioactive sodium and the Geiger counter the course of events in vessels below the surface of the skin can be followed.

Accordingly, it seems worth while to use this type of investigation as a means of studying the effects of drugs used in treatment of peripheral vascular disease. The radioactive material in a few cc. of normal saline is injected into an antecubital vein and its arrival and accumulation in the feet is observed by the continuous recording of the Geiger counter. The injected material is well mixed with the blood in the heart.

As the arterics bring the radioactive substance to the feet and it passes through the capillaries, the sodium diffuses into the extravascular fluid until equilibrium is reached. The Geiger counter registers a steady increase up to this point; the values recorded minute-by-minute can be plotted as a "sodium build-up curve." The shape of this curve depends upon the condition of the main and collateral vessels supplying blood to the feet as well as on the rate of diffusion through the capillary walls. For any individual the curve remains essentially the same on successive tests unless something has been done to affect one of these two factors. Such a test performed immediately after the application of one of the drugs under consideration might be expected to show whether it produced a vasodilating effect.

In a group of patients undergoing treatment, before any drugs were given, a basic radiosodium test was made. Various drugs were then used and the test repeated. Typical results are shown in Figures 1 to 5. Experimental points are indicated for each minute of counting, open symbols represent counts for the left foot and solid symbols represent counts for the right foot. Each chart also shows the "normal range," the region in which the curves fall for normal individuals with no vascular involvement. In some cases several drugs were tested on the same individual.

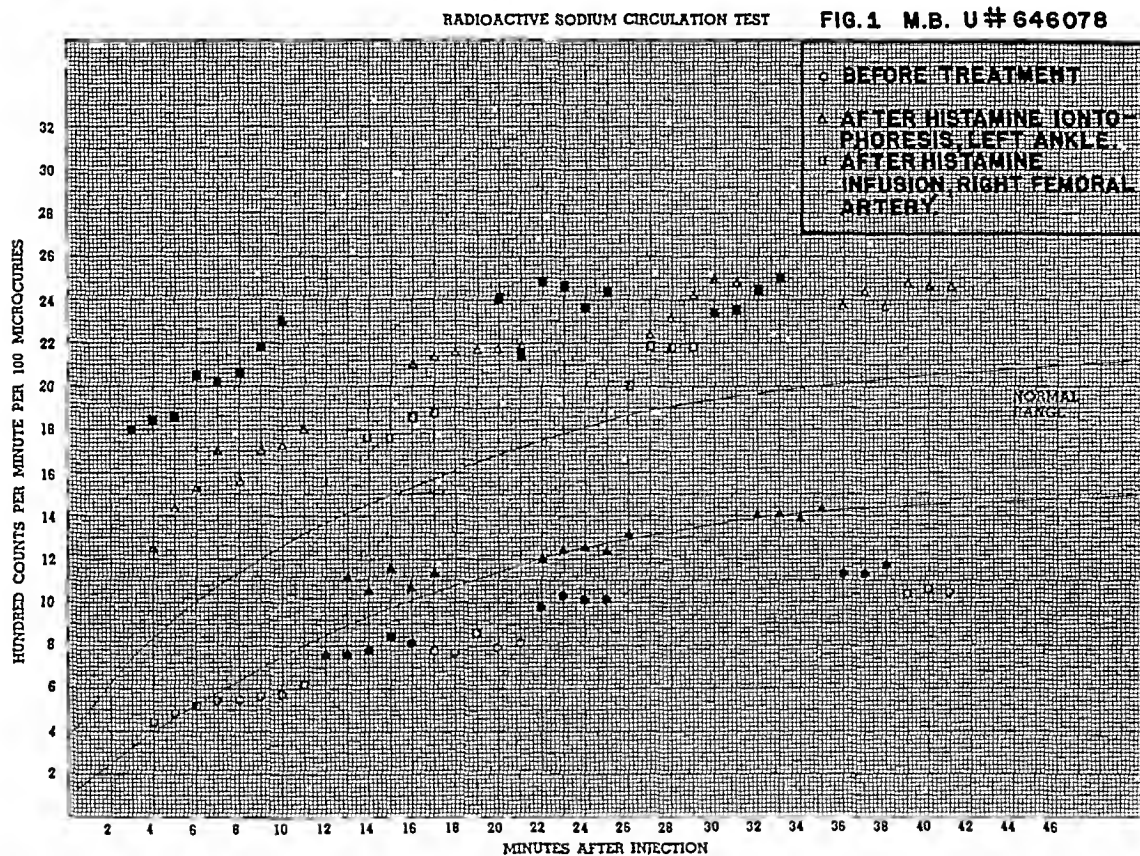
HISTAMINE

By Iontophoresis. Histamine was introduced into the skin of one foot and ankle of each of the patients tested by means of galvanic iontophoresis; the untreated foot served as a control. The histamine-containing ointment "Imadyl" was rubbed into the skin and covered with the negative electrode moistened with normal saline solution. A galvanic current 10 to 20 ma. which without histamine gives no reaction

was administered until the skin reddened or for approximately ten minutes if there was no reaction.

The patient, M. B., Unit No. 646,075 (Fig. 1), with a diagnosis of scleroderma, had a basic curve well below the normal

By Intravenous Injection. In view of this definite response from iontophoresis it seemed desirable to try other routes for the introduction of histamine. The insensitive skin of scleroderma increases the liability to an electric burn. The atrophic and broken

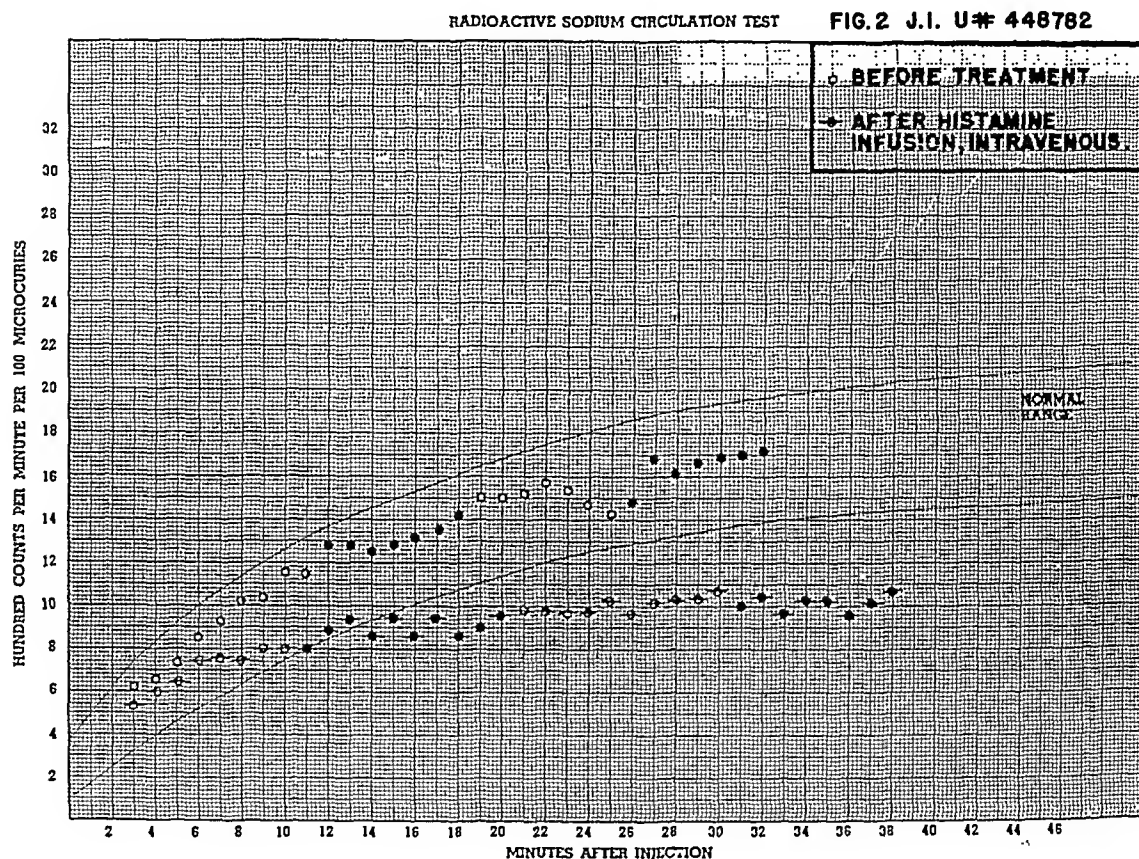


range as shown by the circles. When histamine iontophoresis was completed on her left ankle, the curve for that foot rose well above normal (triangles), while that on the untreated side remained essentially the same as before. The treated skin showed marked rubor and there was a burning sensation. This test was later repeated on the other ankle of the patient with a corresponding rise in that foot. In another case of Raynaud's disease, with the basic curve essentially normal, the rise was definite although not so marked. This patient had a dry, rigid skin which showed little reaction.

skin which is frequently present in arteriosclerotic obliterative arteritis is so sensitive that it often precludes the use of a galvanic current and Imadyl ointment. Histamine has been given intravenously to patients with multiple sclerosis without deleterious effect on blood pressure or pulse.³ Accordingly it was tested in this series. The patient, J. I., Unit No. 448,782, with a diagnosis of thrombo-angiitis obliterans, was given intravenously 1,000 cc. of normal saline containing 2.75 mg. histamine acid phosphate (equivalent to 1 mg. histamine base) at a rate of 140 drops per minute. He quickly

felt a generalized warmth which, however, did not extend to his lower extremities. His face flushed and he complained of headache but there was no color change in his legs or feet. His basic curve (circles, Fig. 2) was in the normal range. The

patient A. B., Unit No. 708,276, who had scleroderma and had shown only moderate response to iontophoresis. The foot immediately became pink, warm and moist. The sodium curve (triangles, Fig. 3) rose sharply from the beginning and was defi-



curve following intravenous histamine (triangles) was much lower. This test was not repeated on another patient because it was believed that in such a procedure a drop rather than a rise was the logical result and it would be of no therapeutic value.

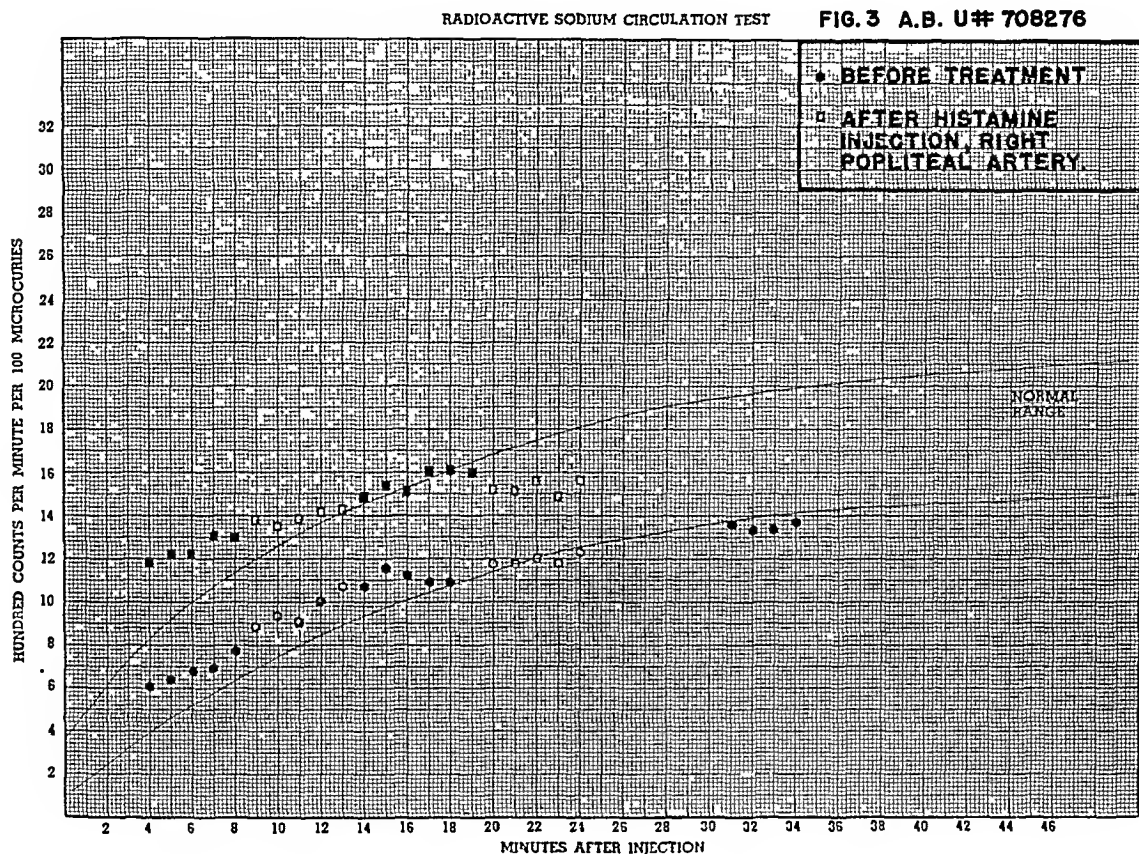
By Intra-arterial Injection. Since local administration of the drug by iontophoresis had produced an effect, it seemed that a more direct placement of the histamine might be more successful than the intravenous route. Accordingly, 0.55 mg. histamine acid phosphate (equivalent to 0.2 mg. histamine base) dissolved in 1 cc. of water was injected into the popliteal artery of

nately higher than the basic curve (circles) for both feet.

It was believed that perhaps a prolonged and milder effect would be more advantageous than a sharp and fleeting one. Accordingly, a drop-by-drop infusion into the femoral artery was used. The histamine was diluted in the same way as when it was administered intravenously, 2.75 mg. histamine acid phosphate in 1,000 cc. of normal saline solution (equivalent to 1 mg. histamine base). This gave a solution with a pH of 6.5. To overcome the pressure in the femoral artery, it was necessary to introduce the solution at a pressure at least

higher than the diastolic pressure in the artery. The ordinary 500 cc. infusion burette was capped by a stopper with two holes which was held down tightly with several strips of adhesive tape. Through one opening in the stopper a piece of glass

anesthetized by procaine, a 2 inch, 18-gauge, short beveled needle was introduced into the femoral artery. The bright red blood and the pulsating thrust into the syringe attached to the needle were evidence of entry into the artery. The syringe



tubing was inserted reaching above the histamine solution. The outer end of the tube was connected to two parts of the ordinary blood pressure apparatus by means of a Y tube. With the arm cuff rolled up snugly and held so with stout rubber bands its rubber tubing was connected to one arm of the Y tube, the tubing of the manometer to the other. A closed circuit was thus established and when the bulb was inflated a positive pressure was created in the infusion bottle which could be measured by the mercury manometer of the blood pressure apparatus.

With the skin and subcutaneous tissue

was detached and the needle was connected with the flask which already had a positive pressure of at least 70 mm. Hg. The pressure was then raised or lowered until the pulsating blood could be seen in the glass-connecting tip during each systole of the heart. Inflow takes place during diastole at the rate of 90 to 120 drops per minute.

The result of such a test in a patient who had responded sharply to iontophoresis is shown by the squares in Figure 1. She received 1.37 mg. histamine acid phosphate in 500 cc. normal saline into her right femoral artery. There was prompt warming and flushing of the skin from toes to buttocks

with slight whealing but without itching. The radiosodium injection was administered as soon as the histamine started to flow. The curve shows a marked immediate rise in the right foot with both feet finally giving values much higher than in the

Several other patients have shown a similar rise in the radiosodium curve and a similar subjective response, varying in degree with the extent of the obliterative process in the larger vessels. On the other hand, in one patient, J. C., Unit No.

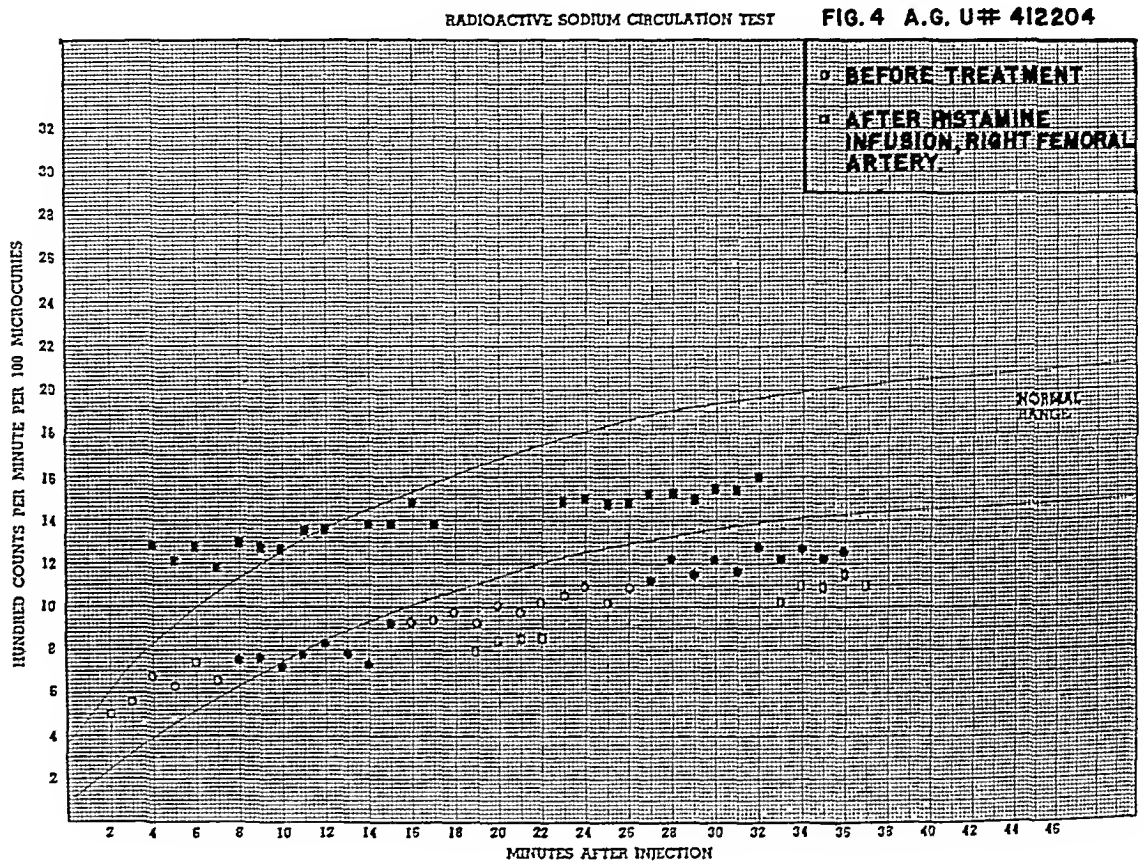


FIG. 4.

basic chart. Figure 4 shows results of the test in patient A. G., Unit No. 412,204, with dermatomyositis and Raynaud's disease. The basic curve was slightly below normal. The curve made during the infusion into the right femoral artery of 300 cc. of normal saline containing 0.3 mg. histamine base shows the right foot brought up into the normal range. The left foot remained at a low range. The skin temperature rose, the muscle temperature fell and the patient noted that this was followed by relaxation of the spastic calf and thigh muscles on the side of the infusion. This relaxation continued for several days.

731,915, with peripheral arteriosclerosis, the curve following this type of histamine treatment coincided with the basic curve.

An attempt was made to reverse the dilatation induced by histamine iontophoresis by the introduction of adrenalin intravenously. It has been shown that adrenalin injected into the skin reduces diffusion from the local blood vessels.⁶ A very dilute solution of adrenalin given intravenously to patients with erythromelalgia relieves a group of characteristic signs and symptoms.¹¹ Case M. B. (Fig. 1) showed a similar group of symptoms following histamine iontophoresis, namely, increase in skin

temperature, marked rubor and a persistent burning sensation. To study the effect of adrenalin on vessels which had been dilated in this manner, she was on two occasions given a venoclysis of 1:250,000 solution of adrenalin hydrochloride immediately following the iontophoresis. The first introduction was administered before the radioactive sodium was given and the second was given twenty-five minutes after the radioactive sodium was injected. In neither case was any effect produced on the graph of either the histamine treated foot or the untreated foot. The curves agree with those for histamine iontophoresis alone, showing no immediate reaction to the drug. There was also no alleviation of the burning sensation.

PAPAVERINE HYDROCHLORIDE

This drug has frequently been used to produce vasodilatation. In these tests 60 mg. were dissolved in 200 cc. of normal saline; 100 cc. was run into an antecubital vein in fifteen minutes. Radioactive sodium was then injected and the remainder of the papaverine allowed to run in at the rate of 25 drops per minute while the sodium curve was being taken. It was believed that in this way a potent and sustained effect of the drug would be obtained. The patient suffered no untoward effects and there were no visual changes in the skin. In four patients thus tested the sodium curves showed no change from the basic curves. One attempt (on M. B.) to alter the curve by a single dose of 0.06 mg. papaverine hydrochloride intravenously also failed to show any effect.

SODIUM CHLORIDE

Intravenous administration of 300 to 500 cc. of 5 per cent solution of sodium chloride is frequently used in patients suffering from peripheral vascular disease. Subjectively, it appears to offer some relief in a number of cases. In five patients receiv-

ing the radioactive sodium test during or immediately following the therapeutic saline injection, no change whatever was observed from the basic curve previously obtained.

COMMENTS

Although the data herein presented are based on a small series of tests, it is believed that they are sufficiently consistent to be informative. Of the substances tested only histamine caused a consistent and marked increase in the rate of diffusion and therefore vasodilatation of the minute blood vessels. The most efficient routes for the introduction of histamine in these tests were found to be through the skin by iontophoresis and intra-arterially. Primary fixation of the histamine in the wall of the blood vessels of the affected extremity, with little or no dissipation into the body, is the result desired. Allen and Crisler² reported that papaverine, mecholyl and histamine could not be fixed by intra-arterial injection. Their graphs for histamine are not convincing. They gave a single rapid injection of the drug and measured skin temperatures. If there was a response, the change in skin temperature would be too transient to register dilatation. Studies of radiosodium curves show that introduction of histamine by iontophoresis causes a marked increase in the diffusion of radioactive sodium. To avoid injury to atrophic, gangrenous or ulcerated skin and with the hope of reaching vessels deeper than those in the subcutaneous layer, the intra-arterial method of administering a dilute solution of histamine was devised. Administered slowly the histamine will be fixed in the tissues and destroyed by the histaminase present. When this method is used, radiosodium graphs following this procedure are definitely above the basic curves for the same individual. It is easy to follow the spreading flush of the skin of the legs and the increase in skin temperature objectively. There is also subjective improvement; the patients

quickly note a sensation of warmth which they have not experienced previously. When the intra-arterial infusion is given at a rate of 70 to 120 drops per minute in patients with marked obstruction of the larger arteries and more slowly to those with

To disregard this warning may cause an untoward experience, as occurred with one patient in this series. The injection was begun satisfactorily but as it later appeared the rate of the infusion was not carefully controlled. The patient's face was markedly

RADIOACTIVE SODIUM CIRCULATION TEST

FIG. 5 A.C. U# 802115

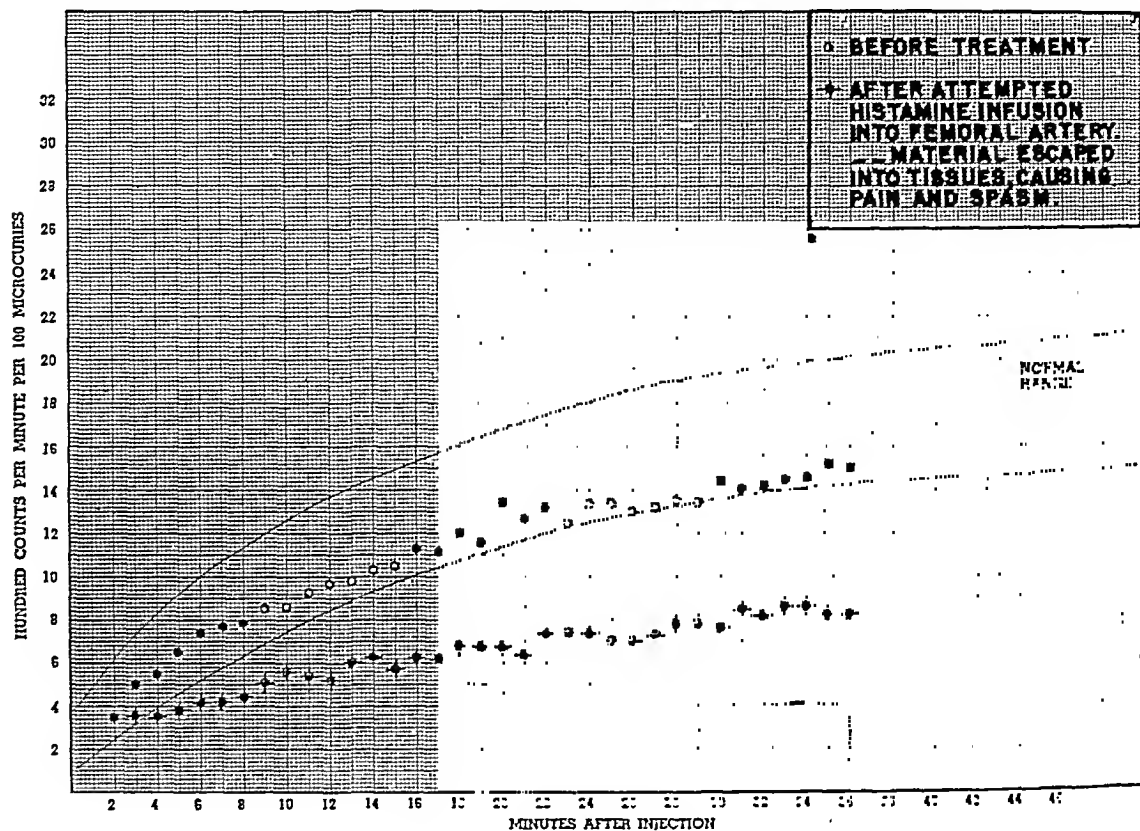


FIG. 5.

moderate obstruction, most of the drug is destroyed by the local histaminase. The optimum amount appears to be 0.7 mg. of histamine acid phosphate dissolved in 250 cc. of normal saline. To date this amount has been given in about ninety treatments with marked objective vasodilatation of the lower extremities and subjective improvement and, with one exception, without accident.

With extensive obliterative disease in the large arteries, up to 500 cc. of similar concentration can be used without danger. If the rate of injection is too rapid, flushing of the face gives forewarning of the escape of histamine into the venous circulation.

flushed and his head had been throbbing for one-half hour when abdominal pain, diarrhea and vomiting suddenly began. His hematocrit showed hemoconcentration. These cleared after a stormy twelve hours following several saline infusions. The sodium build-up curve during the experience remained essentially the same as the basic one. It is not evident why the early part of the curve was not elevated since the pain did not begin at once.

The sensitivity of the vasomotor system to pain may be an important factor in investigations of the type herein discussed. Pain may give rise to unexpected effects which must not be overlooked. This is well

illustrated by the experience with patient A.C., Unit No. 802,115, with a diagnosis of early thrombo-angiitis obliterans in whom the histamine solution failed to enter the femoral artery as intended and infiltrated the subcutaneous tissue instead. Severe pain was felt in the groin and the radiosodium curve was definitely lower than the basic curve instead of higher as was expected after the intra-arterial infusion. (Fig. 5.) This was undoubtedly the result of a reflex spasm set up by the prolonged pain caused by the misplaced drug, and is analogous to the acute capillary spasm which can be observed through the capillary microscope when the arm is pinched or when a blood pressure cuff on the other arm is inflated until pain is caused.

Intravenous histamine not only did not cause an increase in diffusion but induced a lowering of the curve in the one patient tested. The failure to raise the curve can be explained by contrasting the differences in the concentration of the drug, which is greater on direct arterial introduction and less when first diluted by the venous blood before it can reach the arterioles. When the concentration of the drug is low the most sensitive vessels will react first. It is well known that the arterial tree of the lower extremities is least sensitive and that of the head most liable to vasodilatation. The habitual erect posture has been offered as an explanation of this phenomenon. Recent studies¹⁴ on spinal anesthesia may explain the low diffusion curve in the one patient studied. The authors showed that, as expected, a dilatation of the blood vessels in the lower extremities followed the anesthesia. However, vasoconstriction of the blood vessels of the upper extremities took place at the same time. If this compensatory mechanism does not occur, the patient develops signs of shock. The patient receiving histamine intravenously developed dilatation of the blood vessels of the upper half

of his body; his head ached, his face was flushed and his arms felt warm. The drop in diffusion at the feet indicates that the compensating mechanism was effective in his case, as it was in the patients who had a low spinal anesthesia except that the effects in upper and lower extremities were reversed. Furthermore, a similar response has been found by Cook and Sears to occur in dogs after intravenous injection of histamine when radioactive krypton is utilized as an indicator.⁴ They found that the peripheral blood flow in the hind paws fell while coronary circulation showed a marked increase in blood content. In view of these findings, it did not seem desirable to subject more patients to this test since larger doses of histamine theoretically would have been necessary to dilate the blood vessels of the lower extremities and such a dosage was considered too great a risk.

Papaverine administered intravenously, in spite of its stated ability to cause vasodilatation and decrease circulation time, was apparently unable to induce a measurable change in the permeability of the minute vessels of the lower extremities, at least in a single treatment. It might be effective perhaps with lesser involvement of the minute vessels but in the patients in this series, papaverine failed when histamine succeeded. When papaverine is given intravenously, with generalized dilatation of the vascular system, the usual gradient of pressure is maintained although the blood pressure may be lower. In contrast, if the dilatation is localized and a high central pressure is maintained, a higher gradient or differential will be brought about; more blood will be driven into the extremity in this manner. This is the situation when histamine is given intra-arterially.

The reduction in concentration of serum proteins which is known to follow the infusion of 300 to 500 cc. of 5 per cent sodium chloride solution is indicative of hydration of the blood. If this were of sufficient mag-

nitude, it should result in distention of blood vessels with increased capillary permeability. No evidence of this has been found in these tests and it appears that the volume increase is not sufficient. Any benefit from this treatment which is used frequently in thrombo-angiitis obliterans is certainly not the result of an immediate vascular dilatation of sufficient magnitude to be demonstrated by this method.

There are many other factors to be considered in analyzing the mechanism by which vasodilators can alter the permeability of the capillaries. In this study a radioactive sodium isotope was used and so values are established for sodium. It does not follow that other ions or the more complex organic compounds will be affected in the same way. Changes in permeability may be wholly dependent upon variations in action potential and membrane conductance induced, limited or destroyed by enzymatic processes initiated or altered by the drugs used.⁵ From this point of view much work remains to be done.

CONCLUSIONS

1. Patients with scleroderma, thrombo-angiitis obliterans, obliterative arteriosclerotic endarteritis and non-specific arteritis of the minute vessels frequently show a subnormal curve for the diffusion of radioactive sodium from the blood vessels.

2. Histamine administered by iontophoresis or by intra-arterial injection brought about a definite rise in the diffusion curve. When given intravenously in one patient it produced the opposite effect.

3. The dilatation caused by histamine was not reversed by 1:250,000 adrenalin given intravenously.

4. Neither papaverine nor 5 per cent sodium chloride solution given intravenously produced changes in the radioactive sodium curves.

5. Of the drugs tested, only histamine appeared able to produce an immediate increase in capillary diffusion rate as determined by a radiosodium curve taken following a single dose.

6. A method for giving an intra-arterial infusion is described. To date ninety such infusions have been administered.

The authors wish to acknowledge their indebtedness to Miss Charlotte Schmidt for her technical assistance.

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Hypertensive Vascular Disease*

Duration of Life in a Selected Series

DAVID W. BLOOD, M.D. and GEORGE A. PERERA, M.D.

New York, New York

IT is a well recognized statistical fact that hypertensive vascular disease and its sequelae have a detrimental effect on life expectancy. It is also generally accepted that the disease varies greatly in its intensity and rate of progression, with gradations from a benign, asymptomatic form to patients with so-called malignant hypertension with a rapidly fatal outcome. In spite of this knowledge there is a tendency to overlook the fact that a considerable number of patients carry on far better than might be anticipated on the basis of initial observations.

Many attempts have been made to record the course and prognosis of essential hypertension. Keith, Wagener and Barker, whose observations are often used as criteria to compare the results of surgery with medical management, describe four types of hypertensive vascular disease based chiefly on the degree of retinitis.¹ That their data do not give a representative picture is suggested by the fact that 66 per cent of their patients fall into the most serious and advanced group, with only 9 per cent of the entire series alive five to nine years after diagnosis. Earlier studies of prognosis employed varying diagnostic criteria. Some reports included patients followed from the date of the first symptom only, others whose course had already become complicated. Thus Janeway, using a systolic blood pressure of 160 mm. of mercury as his index, declared that hypertensives lived only an average of four

or five years after appearance of their first symptom.² Blackford and Wilkinson grouped only those patients with arterial pressures of 175/100 or over and found that the majority were dead within ten years.³ Even actuarial statistics⁴ fail to give a true picture since subjects studied are predominantly male, in whom hypertension is less common than in women and in general runs a more severe course. It is difficult to obtain a real understanding of the true outlook in this disorder from the available data.

Because of increasing interest in more radical medical and surgical therapeutic measures, it seems timely to re-emphasize the long duration of hypertensive vascular disease in many patients. This study is concerned with a selected group of hypertensive patients whose benign course is in contrast with that pictured in most studies dealing with the natural history of hypertension. The difficulties inherent in attempting to anticipate the course of the disease are illustrated by this report.

CLINICAL MATERIAL

The records of fifty patients were analyzed. All were closely followed as outpatients in the Vanderbilt Clinic and on the wards of the Presbyterian Hospital. The basis of selection included repeated initial blood pressures in excess of 140/90 and at least ten years of subsequent observation. Only such patients were included who were without significant symptoms when first

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y.

TABLE I

STATISTICAL DATA ON FIFTY HYPERTENSIVE PATIENTS FOLLOWED TEN YEARS OR MORE

	Name	Sex	Age When First Seen	Years of Observation	Initial B.P.	Latest B.P.	Cardiac Failure	Renal Failure	Cerebral Accident	Now Living or Dead	Final Comments
1.	W. F.	F	38	10	230/140	210/130	L	Living and well
2.	E. S.	F	49	10	150/90	170/100	+	D	Cardiac insufficiency first evident 9 yr. before death
3.	H. N.	M	55	11	140/98	220/110	+	..	+	D	Died following cerebral hemorrhage
4.	M. H.	F	33	11	268/160	295/170	+	D	Died following cerebral accident
5.	M. K.	F	41	12	240/120	220/130	+	D	Died following cerebral accident
6.	S. K.	F	35	12	185/100	260/140	+	L	Recent cardiac insufficiency
7.	E. E.	F	22	12	160/120	160/132	L	Living and well; 3 normal pregnancies after development of hypertension
8.	V. S.	F	36	13	170/110	200/120	+	D	Died of cardiac insufficiency
9.	M. H.	F	45	13	178/96	200/100	L	Moderate headaches
10.	J. K.	F	34	13	185/100	260/140	L	Living and well
11.	C. B.	F	38	13	170/100	170/90	L	Living and well
12.	M. S.	F	49	13	200/95	270/120	+	D	Died 11 yr. after first episode of cardiac insufficiency
13.	I. M.	M	32	13	180/140	230/120	+	L	Mild cardiac insufficiency 4 yrs. ago; no symptoms thereafter
14.	E. S.	M	53	14	185/115	240/130	D	Postoperative death
15.	S. M.	M	33	14	185/105	185/120	+	D	Died of myocardial infarction
16.	E. S.	M	53	14	185/115	210/130	+	D	Unexplained death 3 yrs. after development cardiac insufficiency
17.	E. W.	F	55	14	280/125	278/140	+	..	+	L	Recent cerebral accident
18.	L. H.	F	49	14	200/120	270/140	L	Living and well
19.	A. R.	F	48	14	158/96	215/105	L	Headaches, no other symptoms
20.	G. S.	F	33	14	155/100	225/125	L	Living and well
21.	M. T.	F	50	15	195/100	190/120	L	Hypertension known 13 yrs. before first visit; has never had hypertensive symptoms
22.	A. R.	F	35	15	160/90	140/110	+	+	..	D	Died in failure 7 yrs. after first cardiac symptom
23.	L. F.	F	38	15	200/120	165/100	+	L	Cardiac insufficiency for 12 yr.
24.	S. R.	F	37	16	230/130	275/145	+	D	Death attributed to arteriosclerosis
25.	A. D.	F	47	16	162/90	210/90	L	Living and well; never had significant symptoms
26.	R. T.	F	29	16	190/110	260/130	+	..	+	D	Died following cerebral accident
27.	A. W.	F	40	17	170/90	180/110	L	Living and well
28.	R. S.	F	20	18	144/100	200/114	L	Rare headaches; no other symptoms
29.	V. A.	M	30	18	170/100	180/120	L	Living and well
30.	M. H.	F	32	18	196/100	190/105	+	L	Recent ankle edema only
31.	S. B.	F	39	18	180/100	175/120	+	L	Exertional dyspnea for the past 4 yr.
32.	J. B.	F	50	19	170/100	120/85	L	Living and well
33.	E. P.	F	45	19	200/90	240/130	+	+	..	D	Uremia and cardiac insufficiency
34.	A. T.	F	47	19	165/100	200/100	L	Living and well
35.	L. T.	F	45	19	170/110	160/84	+	L	Recent ankle edema only
36.	F. M.	F	50	20	150/98	190/110	L	Occasional headaches only complaint
37.	D. C.	F	40	20	160/105	200/160	L	Moderate headaches; otherwise well
38.	J. R.	M	57	20	165/100	210/110	+	D	Unexplained death; never had hypertensive symptoms
39.	C. M.	M	48	21	180/120	170/100	L	Living and well

TABLE I.—(Continued)

	Name	Sex	Age When First Seen	Years of Observation	Initial B.P.	Latest B.P.	Cardiac Failure	Renal Failure	Cerebral Accident	Now Living or Dead	Final Comments
40.	A. C.	F	26	21	150/110	140/95				L	Living and well
41.	A. A.	F	43	21	170/100	195/100				L	Occasional headaches and palpitations
42.	M. S.	F	42	21	165/105	210/115	+			L	Mild cardiac insufficiency for past 3 yr.
43.	A. P.	F	45	22	200/100	250/100				L	No symptoms; slight cardiac enlargement
44.	L. H.	F	46	23	200/110	210/120	+			L	Well except for moderate ankle edema
45.	H. M.	F	38	23	165/115	160/95				L	Intermittent headaches; no abnormal signs other than hypertension
46.	V. R.	F	28	23	165/110	170/90	+				Rare headaches the only complaint
47.	A. K.	F	39	23	155/95	160/80	+		+	D	Died after cerebral accident; previously asymptomatic
48.	L. S.	F	30	23	180/120	200/110			+	L	Living and well 11 yr. after cerebral accident
49.	B. O.	F	43	27	185/120	190/100				L	Living and well
50.	G. L.	M	41	27	200/110	180/94				D	Sudden unexplained death after 27 yr. without symptoms
Total and Averages		M 9 F 41	42	17	182/108	204/115	22	2	7	L 34 D 16	

seen and who showed no evidence of cardiac, renal or cerebral involvement. A few patients in the series had mild headaches as their only complaint. All who were later shown to have a primary renal disturbance with secondary blood pressure elevation were excluded, as were those patients initially exhibiting more than minimal, transient albuminuria. The degree of hypertension in the group as a whole suggests that the disease had been well established prior to the initial observation.

RESULTS

The results are summarized in Table I.

Age. The average age at the time of first observation was forty-two years, the youngest patient in the series being twenty-two years of age and the oldest fifty-seven. The average age was only slightly higher for males (forty-four years) than for those in the

series as a whole. Those patients followed until their death showed no major differences in their average age when first seen (forty-four years) in comparison with the group still living.

Sex and Race. Forty-one (82 per cent) of the patients were female and 9 (18 per cent) were male. The racial distribution was comparable to that of the average clinic population.

Years of Observation. The average length of observation was seventeen years, varying from ten years and three months to twenty-seven years and one month. Thirteen of the fifty patients were observed for a period of over twenty years and twenty-nine of the patients were followed for more than fifteen years.

Deaths. Sixteen (32 per cent) of the fifty patients died during the course of observation, the majority as a result of cardiac

complications or following a cerebral vascular accident.

Blood Pressure. A composite picture of the systolic and diastolic blood pressure trends is shown in Figure 1. Although there was considerable variation in individual

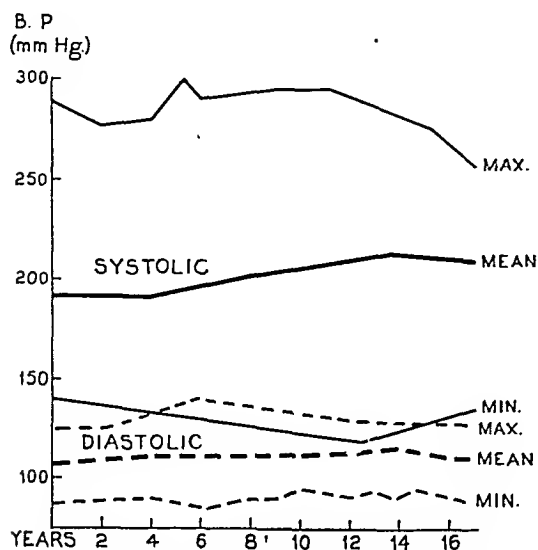


FIG. 1. Mean, maximum and minimum systolic and diastolic blood pressures of fifty hypertensive patients.

patients, the general tendency of the hypertension was to increase very slowly throughout the years of observation. The average initial blood pressure was 182/108 mm. of mercury while the average pressure at the time when last observed was 204/115. Blood pressure determinations were obtained during clinic visits by different observers and under varying conditions, hence evaluation of these readings should take into account personal variations in measurement.

Symptoms and Signs. These have been analyzed under the following headings with emphasis on their relationship to prognosis.

Patient's Complaints. A conspicuous number of patients during the course of their disease complained of fatigue, nervousness, dizziness, palpitation, insomnia and weakness in addition to specific symptoms to be further enumerated. There was no relation of these complaints to the subsequent course of the disease.

Cardiac Insufficiency. Twenty-two of the fifty patients at some time developed manifestations of congestive failure such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea and ankle edema. In most of these patients the insufficiency came late in the course of the disease. The average length of observation following the first onset of cardiac insufficiency was seven years, the longest period being fifteen years and eleven months. Eight (39 per cent) of this group with congestive failure died during the course of observation, the average age of survival from the first symptom being eight and one-half years.

Cardiac Pain. Nine (18 per cent) of the patients complained of pain of cardiac origin at some time. The average period of observation from the onset of pain was five years, the longest being nine years and five months. Only one of this group is still living.

X-ray Evidence of Cardiac Enlargement. Thirty-three (66 per cent) of the patients in the series showed an increased cardiac area by x-ray during the course of their disease. Of these, ten (33 per cent) died during the observed period, with an average survival of nine years. The average period of observation for the entire group from the first sign of enlargement was ten years, the longest being twenty years and three months.

Electrocardiographic Changes. Eighteen (36 per cent) of the fifty patients had electrocardiographic changes indicative of myocardial damage. Two of these changes occurred just prior to death. The average length of observation was six and one-half years, the longest being seventeen years and four months. Eight (43 per cent) of the group were followed until death with an average survival period of seven years.

Renal Changes. Only two patients showed evidence of nitrogen retention. One of these died from cardiac failure seven years later; the second patient died from uremia a few months after nitrogen retention was appar-

ent. Twenty-nine (58 per cent) of the fifty patients developed persistent albuminuria during the course of their disease. The average period of observation from the onset of albuminuria was seven and one-half years, the longest being twenty-seven years and one month. Eight (27 per cent) of the group died during the period of observation, the average period of survival being eight years.

Cerebral Changes. Seven cases (14 per cent) developed a cerebral vascular accident during the observed course of the disease. In six of these the cerebral involvement resulted in death. The remaining patient had a cerebral accident after twelve years of known hypertension and was without signs or symptoms for eleven years and was well when last seen in the clinic.

Retinal Changes. Thirty-three patients (66 per cent) had retinal changes of some degree during the course of their disease. The average number of years of observation from the onset of arteriovenous compression was ten years but it was present in one patient twenty-three years and five months before the date of the last observation. Eight (24 per cent) of the group died during observation with an average period of survival of nine years. Only seventeen (51 per cent) of the thirty-three patients with retinal changes developed more severe damage as indicated by hemorrhage, exudate or papilledema. The average period of observation in this group was six and one-half years but one patient survived twenty-one years and six months after extensive exudate had been seen. Nine (53 per cent) of this group died during observation, the average survival being seven years. There were several patients in the group showing retinal exudate and hemorrhages whose retinitis regressed conspicuously during the course of their disease.

Headaches. Thirty-seven of the fifty patients (74 per cent) complained of headaches

at some time during the course of their disease. Most of these were of a minor degree and even the more intense headaches were not constant and often disappeared completely after months or years of great severity. It was of interest that a few patients, with no familial or previous history of idiopathic migraine, complained of headaches which assumed a typical migraine pattern. There was no correlation whatsoever between the frequency and intensity of the headaches, the height of the blood pressure or the course of the disorder.

Final Observations. Sixteen (32 per cent) of the patients in this series died, while twenty-four (48 per cent) were living and free of significant symptoms at the last observation. The remainder had more severe complaints or exhibited signs or symptoms of cardiac insufficiency.

COMMENTS

This series of fifty patients who were asymptomatic and had uncomplicated hypertensive vascular disease when first observed, and who were followed for at least 10 years, is obviously a selected one. It gives no consideration to hypertension in its more progressive forms or to patients who first consult their physician because of complicating signs and symptoms. Although the present study gives no statistical information as to its frequency, it does indicate, however, that long survival is not a rarity. The majority in this group showed well established hypertension at the time of initial observation and may have had an elevation of blood pressure for an indefinite period prior to observation.

Except for the mild character of their disease, the patients studied in this group appear to be comparable with other reported series of patients with respect to age, sex distribution and general characteristics. It is significant that in the group studied the initial level of the arterial pressure did

not seem to be associated either with symptoms, rate of progression or with the subsequent development of major cardiovascular complications. It was also apparent that palpitation, headaches, x-ray evidence of cardiac enlargement and retinal arteriovenous compression bore no correlation to the subsequent course.

A steadily rising blood pressure over a period of time, cardiac pain or insufficiency, electrocardiographic signs of myocardial damage, progressive renal damage, cerebral vascular accidents, retinal hemorrhages, exudate or papilledema were, in general, indicative of a relatively short life expectancy, but in individual patients a long period of survival followed such complications.

Thus, it is evident that in hypertensive patients, even in those who may complain of headaches, nervousness and palpitation, irrespective of whether there is cardiac enlargement, minor electrocardiographic change, minimal albuminuria and early retinal change, a definite prognosis should not be made since such a patient may live for one, two or more decades before fatal complications appear. Without repeated observations over a period of months or years, one is not justified in foretelling the future trend or in differentiating a relatively benign from a more malignant process. The indications for and the evaluation of the results of such procedures as sympathectomy must take into consideration the not infrequent long period of survival and comparative well being of many patients.

CONCLUSIONS

1. An analysis was made of fifty patients who, when first observed, exhibited asymp-

tomatic and uncomplicated hypertensive vascular disease and were subsequently followed for at least ten years.

2. The average length of observation in this selected group was seventeen years, the longest period exceeding twenty-seven years.

3. It was found in the group studied that the initial height of blood pressure, symptoms such as headaches and palpitation, the presence of cardiac enlargement, minimal albuminuria, minor electrocardiographic changes and retinal arteriovenous compression bore no relationship to prognosis.

4. Essential hypertension may be compatible with many years of survival and well being.

5. The favorable outlook for some patients with hypertension should be considered in evaluating the indications for and the results of such therapeutic procedures as sympathectomy.

The authors are greatly indebted to the Albert and Mary Lasker Foundation for the means to carry out this study.

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Clinical Aspects of Coronary Insufficiency*

ROBERT L. LEVY, M.D.

New York, New York

DISARRANGEMENT of function is responsible for the symptoms of disease and may exist without demonstrable anatomic lesions. Coronary insufficiency is a functional disturbance, associated most frequently with atherosclerosis of the coronary arteries and its sequelae. Less commonly, it is caused by syphilitic stenosis or occlusion of the coronary ostia, to aortic valvular disease or to a disorder in the rate or rhythm of the heart such as paroxysmal tachycardia. Indirectly, it can be brought about by a systemic disease of which severe anemia is an example. It is not dependent for its occurrence upon specific structural changes. It results when the blood delivered to the myocardium is inadequate, in quality or quantity, for effective performance of the work required of the heart. As a consequence of ischemia and anoxia, signs and symptoms appear which delineate various clinical pictures in a manner which serves to distinguish one from another.

In the discussion which follows, no attempt will be made to give an exhaustive survey. For a number of years clinical studies of coronary heart disease have been made in the Department of Cardiology at the Presbyterian Hospital. Some of these observations will be reviewed and correlated.

TERMINOLOGY AND CLASSIFICATION

To the various syndromes which may result from impairment of the coronary blood flow a variety of names has been applied. Their multiplicity has brought confusion rather than clarity and has in-

creased the difficulties of accurate diagnosis. Angina pectoris, anginal pain, cardiac pain, coronary occlusion, coronary thrombosis, cardiac infarction, subacute myocardial infarction or necrosis, coronary failure and coronary insufficiency are designations employed loosely and, too often, in the absence of criteria that are sufficiently definite for differentiation. To insist upon a logical terminology is not mere quibbling; it is of basic importance. Without clear definition of terms, there can be no understanding of the conditions to which they are applied. As a result, diagnosis lacks precision and effective guidance of the patient is impossible.

The classification of disorders of the coronary arteries here presented is based upon disturbances of function and structure; both are concerned in determining the clinical features.¹ All types are regarded fundamentally as manifestations of coronary insufficiency so that a unity of concept is maintained. Because the disorders due to atherosclerosis comprise over 90 per cent of the entire group, consideration will be given only to them; but the principles involved apply also to those of different etiology.

Insufficiency of the coronary circulation may be divided properly into two main groups: acute and chronic. (Fig. 1.) The manifestations of the acute form are more dramatic and varied than those of the chronic variety and a larger share of attention has been given to them. From the point of view of management, the crucial point to be determined is whether recent infarction has occurred.

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Medical Service of the Presbyterian Hospital. Read at the Centennial Celebration of the University of Buffalo, Buffalo, N. Y., October 1, 1946.

The first subgroup of the acute variety comprises those cases in which no recent infarction has taken place and there is no evidence of recent coronary occlusion. The most common manifestation of acute coronary insufficiency of this type is the familiar

occlusion of a coronary branch or to marked narrowing of one or more branches which has been present for some time and which eventually leads to such a degree of malnutrition of the myocardium that softening takes place.³ The most common symptom

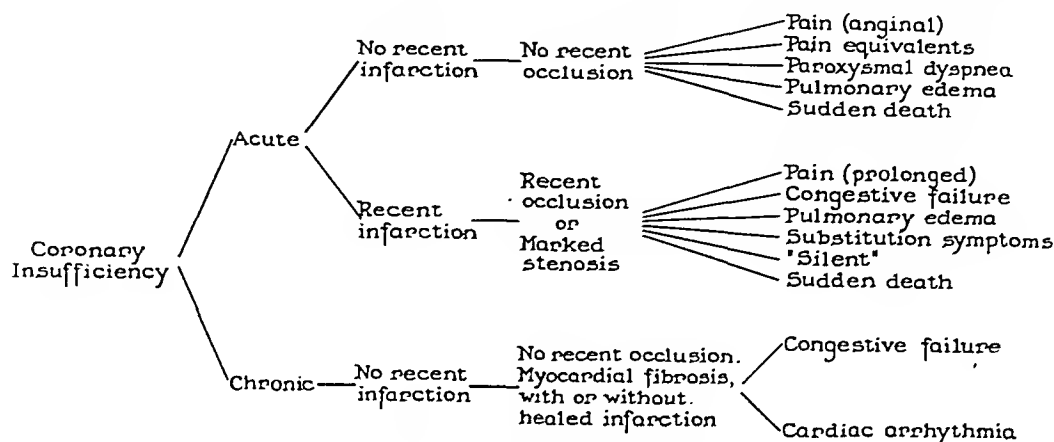


FIG. 1. Clinical types of coronary insufficiency and their manifestations.

paroxysm of anginal pain, but certain individuals are made aware of an impaired coronary blood flow by various pain equivalents. Among these are a sense of pressure or tightness across the chest, a sudden feeling of extreme weakness or, less commonly, profuse sweating, particularly about the head and neck. The symptoms sometimes are referred to the abdomen and are mistakenly regarded as due to some disorder of the digestive tract. Discomfort may be felt only in the shoulders, neck or back. In some cases, there is paroxysmal dyspnea without evidence of moisture in the lungs. In others, acute pulmonary edema accompanied by extreme dyspnea may result from the sudden onset of left ventricular failure. Sudden death may occur during sleep or following sharp exertion; or the heart may cease unexpectedly after excitement or emotion, whether this be pleasant or associated with grief or nervous shock. To this condition has been applied the term "acute, fatal coronary insufficiency."² The hearts of such patients show varying degrees of coronary sclerosis and narrowing but not necessarily evidence of recent thrombosis or infarction.

Infarction may be caused by rapid

of acute obstruction is prolonged, agonizing pain, relieved only by large doses of an opiate. Often final closure is preceded by a succession of rapidly recurring anginal paroxysms, occurring even at rest, which furnish warning that occlusion is imminent. The diminished reserve of a previously impaired myocardium may be so far reduced by the added injury that congestive failure appears. Pulmonary edema sometimes ushers in the attack. As in the case of anginal pain, various substitution symptoms may mask the true nature of the basic pathologic process. Examples of these are mild substernal pressure, general weakness, sweating about the head and neck or nausea and vomiting; sharp epigastric pain may arouse the suspicion of an acute abdominal emergency. Shutting off of a coronary branch may be unaccompanied by any discomfort and may occur "silently," particularly in older persons debilitated by long-standing disease or in those suffering from surgical shock. Sudden death may result from ventricular fibrillation or standstill of the entire heart.

In chronic coronary insufficiency, no recent cardiac infarction has occurred. There is extensive myocardial fibrosis and

not infrequently the heart muscle shows scars indicating the sites of healed infarcts. The patient may have had no symptoms and the lesions described are found at autopsy to the surprise of the clinician and the ill concealed pleasure of the pathologist. But often myocardial fibrosis leads to cardiac hypertrophy and to varying degrees of congestive heart failure. This clinical picture, formerly described as chronic myocarditis and subsequently as non-valvular heart disease, is produced by prolonged ischemia of low degree and consequent malnutrition of the heart muscle. Sometimes a cardiac arrhythmia, particularly auricular fibrillation or auriculoventricular heart block, affords evidence of a damaged and functionally disordered heart muscle.

It has already been said that the most important diagnostic problem for the clinician is to determine whether recent infarction of the myocardium has taken place. Its cardinal features are well known.⁴ Fever occurs in almost every case, so that when the presence of a fresh infarct is suspected the rectal temperature should be taken and recorded twice daily for several days. Elevation of the temperature usually occurs on the second day and, in the uncomplicated case, persists, on the average, for a week. Increase of the sedimentation rate of the red blood cells likewise is a sign present in most instances; when the area of infarction is very small or congestive failure is present, the rate may be normal. The increase appears, as a rule, on the third or fourth day and persists for about four weeks unless some complicating condition, such as pulmonary infarction, causes a continued elevation. In mild cases, the sedimentation rate may return to a normal level within a week or ten days. Leukocytosis is observed earlier than the change in sedimentation rate, appearing often within the first twelve hours and almost invariably, if it occurs at all, in the course of the first day. It persists, on the average, for five days. Occasionally, no increase in the white count is found but slight rises above 10,000 per cu. mm. may

be significant regardless of a corresponding relative increase in the polymorphonuclear cells.

Tachycardia and a fall in systolic blood pressure are found in over 80 per cent of patients. Changes in the form of the electrocardiogram are present in about 90 per cent if serial records are taken on successive days and several precordial leads are employed. In our experience, leads CF_2 , CF_4 and CF_5 have been the most helpful when the diagnosis was in doubt. A gallop rhythm, or reduplication of the first sound at the apex, is heard in about 30 per cent of the patients. A pericardial friction rub is heard in only 20 per cent. It is often of short duration and may come and go in the course of the day. When present, it aids in diagnosis; its absence does not weight the evidence against the existence of infarction.

EVOLUTION OF CORONARY HEART DISEASE

If electrocardiograms are taken at frequent intervals in patients known to have coronary sclerosis, it is not uncommon to discover varying patterns without associated symptoms. Such an occurrence need not occasion surprise, for it is in accord with the concept that arterial degeneration is inherently a progressive process. Even several main coronary arteries may be occluded before the final illness in the absence of anginal pain or congestive failure. This has been clearly demonstrated by Blumgart and his associates who correlated the clinical manifestations with the pathologic lesions in hearts injected and dissected at autopsy.⁵

It has been possible to make a similar correlation between the course of the disease and the electrocardiographic pattern in patients who have been followed for long periods of time and who, while striking changes have occurred in the form of the graphic records, have experienced no discomfort. These changes may be progressive, indicating advancing lesions due to increasing impairment of the coronary bed, or regressive, pointing to the development of a

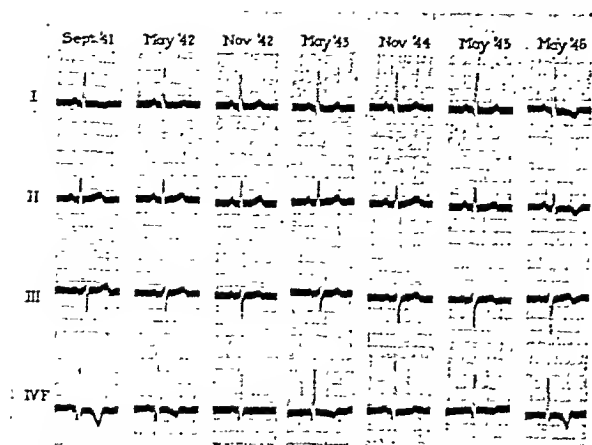


FIG. 2. Male, aged sixty years when first seen. Electrocardiograms show healing of cardiac infarct, instability of coronary circulation and occurrence of further occlusion, infarction and fibrosis. Patient asymptomatic throughout and leading an active life.

collateral circulation. Several instances of this sort have been reported in detail in an earlier paper.⁶ In the following case a series of electrocardiograms portrayed, in turn, healing of a cardiac infarct, instability of the coronary circulation and the occurrence of further occlusion and infarction while the patient, unaware of these changing conditions in his heart, led a full and active life.

CASE REPORTS

CASE 1. A. K., male, aged sixty years when first seen, was a business executive. He stated that he had an attack of coronary occlusion six months previously. His general health had been excellent and he never had any previous cardiac symptoms. He was in the habit of spending his vacation on his ranch in Colorado at an altitude of 7,800 feet where he rode horseback regularly, worked in the fields and never experienced any discomfort.

The symptoms of the coronary episode evidently were mild and pain was slight. He remained in a hospital for ten days and at home for ten weeks. Activity was gradually resumed and at the time of his first visit to the author, he was at work although at a slow pace. His only complaint was that following any unusual exertion, particularly after a meal, he felt a sense of substernal pressure.

The examination showed slight retinal sclerosis. The heart was not enlarged on percussion. The rhythm was regular; the rate was 60. The

sounds were soft and a faint systolic blow was heard at the apex. There was also a short systolic murmur at the aortic area. The blood pressure was 154/86.

Orthodiagraphic measurement showed no cardiac enlargement. On fluoroscopic examination the border of the left ventricle appeared to be rather straight and the aorta was tortuous although not dilated. The electrocardiogram was characteristic of healed anterior infarction. (Fig. 2.)

The patient, who lives in a distant city, has been followed at intervals for the past five years. There has been no further discomfort in the chest. He has been working regularly, taking a brief rest on a couch each day after lunch. He has spent his holidays on his ranch and has ridden horseback. The blood pressure has ranged from 142 to 150 systolic; 80 to 88 diastolic. At the last examination, made a few months ago, he looked considerably younger than his sixty-five years.

A series of electrocardiograms showed interesting variations in view of the absence of any symptoms. (Fig. 2.) Between September, 1941 and November, 1942, there was a progressive trend toward normal. The T wave in lead I, which was inverted in the first record, became upright and T_{4F} became isoelectric. Small Q waves persisted in these same leads. In the records of May, 1943, November, 1944 and May, 1945, T_{4F} was variable, shifting from negative to positive and then to negative again although, during this period, the form of the limb leads remained constant. In May, 1946, striking changes were observed. The T waves in leads I, II and IVF were sharply inverted, indicating almost certain closure of a coronary branch located predominantly on the anterior aspect of the heart, with infarction and subsequent fibrosis. At this time, he stated that he felt particularly well and could not recall having had any pain in the chest or a mild digestive upset even after direct questioning. A recent letter states that he has continued in good health.

DIAGNOSIS OF CORONARY INSUFFICIENCY

In no other disorder is a good history of more help than in the recognition of disturbances in coronary blood flow. Obviously, the efficacy of the blood supply to the myocardium cannot be measured directly;

the most reliable guide is the ability of the heart to perform its work, expressed in terms of the patient's sensations. No matter how well the story of disability is related by a medical colleague, it cannot give the same information as when it is obtained directly from the sufferer. The impression gained by the physician from careful questioning of the patient often furnishes the clue to the entire situation. In addition, such a personal interview establishes a relationship which is invaluable throughout the subsequent period of management.

The patient's account of his trouble may be the only available evidence on which to base an opinion since the examination not infrequently reveals no signs of disease. Sometimes the electrocardiogram shows changes which at once fix the site of the difficulty but here, as in the case of the history, the attending physician should make the interpretation. He must be aware of the wide range of the normal; too often a patient is advised to live as a cardiac invalid because of some minor graphic variation. On the other hand, the recognition of significant early abnormality may lead to preventive measures of vital importance. The use of multiple precordial leads has added to the accuracy of diagnosis in doubtful cases.

Cardiac enlargement, occurring in the absence of hypertension, valvular deformity or other obvious causes, should always arouse the suspicion of coronary disease. Unless enlargement is marked, percussion or location of the apex beat cannot be relied upon for the determination of the size of the heart and recourse must be had to orthodiagraphy or teleroentgenography. The establishment of normal standards for heart size, as indeed for any biologic variable, is difficult and the results are subject to error. Fluoroscopy often gives valuable information with respect to the size and shape of the various chambers and the character of their pulsations. In the author's judgment, the most useful measurement is the transverse diameter, as determined in the orthodiagram or teleroentgenogram, compared to the predicted transverse diameter com-

puted by the Hodges-Eyster formula which takes into account the weight, height and age of the subject.⁷ If the actual transverse diameter exceeds the predicted value by more than 1 cm., it is usually safe to infer that the heart is enlarged. A greater allowance is sometimes permissible when the subject is markedly obese and the heart is in an extreme transverse position. The cardiothoracic ratio, still sometimes employed, has been an unreliable index in our hands.

THE ANOXEMIA TEST

It is sometimes difficult to appraise the significance of pain in the chest and to locate its point of origin. The physical examination and electrocardiogram may fail to reveal evidence of cardiac disease. To determine whether the heart is the source of discomfort, because of an inadequate coronary circulation, is a matter of first importance.

We have been particularly concerned, in our laboratory, with the development of the anoxemia test.⁸ This furnishes an objective index of the functional efficiency of the coronary circulation. It is based on the observation that induced oxygen want produces changes in the form of the electrocardiogram which are more pronounced in patients with coronary insufficiency than in normal subjects. Specific criteria have been evolved which make possible the distinction between a positive and a negative response.

Apparatus. A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnishes an unvarying concentration of oxygen in the inspired air. The gas flows through a humidifier into a rubber bag which is kept full but not distended. Two flutter valves are incorporated into the system in such a way that rebreathing is avoided. A second tank, containing 100 per cent oxygen, is also in the circuit so that, if desired, anoxia can be quickly relieved by turning a needle valve.

Procedure. The subject is allowed to rest quietly in bed for a period of at least thirty

minutes. He is told that if pain is experienced in the chest, arms or abdomen during the test, he should at once raise his hand so that the test may be terminated. Electrocardiograms are taken with four leads; the standard leads and the precordial lead commonly designated *rvf* are used. The records are made just before the start of the test and at intervals of ten and twenty minutes thereafter. The standard period of inhalation is twenty minutes but if pain is felt or there are signs of an undesirable reaction, an electrocardiogram is taken at once and 100 per cent oxygen is then administered for one or two minutes. If distress is severe, 100 per cent oxygen is given immediately without waiting to take the electrocardiogram.

In each lead the deviation of the RS-T junction is measured in millimeters and the direction of the T wave is noted.

Criteria of a Positive Test. The result is positive when any one of the following is found: (1) the arithmetic sum of the RS-T deviations in all four leads (*I*, *II*, *III* and *IVF*) is greater by 3 mm. or more than in the control; (2) there is partial or complete reversal of the direction of the T wave in lead *I*, accompanied by an RS-T deviation of 1 mm. or more in this lead or (3) there is complete reversal of the direction of the T wave in lead *IVF*, regardless of any associated RS-T deviation in this lead.

Precautions. The control record should be developed and read before the test is begun in order to be certain that a recent cardiac infarct is not present. If there is doubt on this point, it is best not to proceed. In addition, the test should not be performed under the following circumstances: (1) if it has been done on the patient within the past twenty-four hours; (2) if congestive failure is present or (3) if cardiac infarction is known to have occurred within the preceding four months.

Unpleasant Effects. In the course of a series of studies of induced anoxemia, the test was given to patients with cardiac disease of different types and varying degrees of severity. Vasovagal attacks were occasionally observed. These consisted of slowing of

the heart rate, fall in blood pressure, coldness of the skin, pallor and sweating. Mild convulsive seizures, dyspnea and hyperventilation were also noted in a few cases. Barnes and his associates have recorded ventricular premature contractions, nodal rhythm and brief cardiac standstill during the anoxic period.⁹

Acute pulmonary edema occurred in three of our patients with prompt recovery following the hypodermic injection of morphine, inhalation of oxygen and rest overnight. In three elderly patients with sclerotic cerebral vessels, there was mental confusion which lasted less than fifteen minutes.

In two of our patients, the physician in charge failed to read the control electrocardiogram before making the test. As a result, one of the patients died suddenly during the procedure. Both the electrocardiogram and the autopsy showed fresh infarction of the myocardium. In the second patient, ventricular tachycardia appeared after seven minutes of anoxemia. The arrhythmia persisted in spite of intramuscular injections of quinidine and oxygen therapy in a tent. Death occurred four hours later. In this instance, likewise, the control record clearly indicated a recent infarct. Autopsy was not done.

Results. In the Department of Cardiology at the Presbyterian Hospital, the test has been performed several thousand times. A detailed account of its use in 289 cases at the Mayo Clinic has been published recently by Pruitt, Burchell and Barnes.⁹ It has been employed by the Medical Departments of the Army and Navy. At the New York Hospital, Stewart has had a wide and untroubled experience with it.¹⁰ In Nylin's clinic, in Stockholm, more than 1,000 tests have been made; Björck has published an account of 350 of these performed on 326 patients.¹¹ Data are accumulating rapidly from various sources.

In any large series of cases, the percentage of positive tests will depend on the nature of the material studied. Instead of quoting percentages, it seems more profitable to

make certain general statements which appear justified by the facts so far available.

A positive reaction may be regarded as a sign of coronary insufficiency. A negative reaction does not exclude disease of the coronary arteries. As is the case in any functional test, there must be a significant diminution in reserve before this can be demonstrated objectively. It cannot be too strongly emphasized that no clinical importance should be ascribed to a negative result.

In our experience, the occurrence of pain during a test which is electrocardiographically negative, is worthy of attention. If discomfort is similar in character to the original complaint, there is evidence that anoxia is capable of reproducing it. Follow-up of this group of patients has shown that a large percentage later developed unmistakable symptoms and signs of coronary heart disease. In many of them, the anoxemia test subsequently became electrocardiographically positive.

In the opinion of Barnes and his associates, pain induced by anoxemia is of no greater diagnostic value than the patient's description of his symptoms. This viewpoint is not supported by our studies. Obviously, the observer must make the distinction between pain of cardiac origin and the minor discomfort of an apprehensive subject. Usually this is not difficult. No significance should be attributed to the complaint of pain when payment for disability is involved.

The result of a test during which pain occurs but electrocardiographic changes are absent must be reported as negative. Patients in this category should be followed with special care and managed conservatively.

The test does not yield a quantitative expression of the degree of coronary insufficiency but in a given patient, there may be variations which parallel the clinical course. With improvement associated with the development of a collateral circulation, a positive test often becomes negative. Conversely, reduction in coronary flow may change a negative into a positive response.

It is not possible to predict, on the basis of the result, the likelihood of future coronary occlusion. The test affords an index, within undefined limits, of the adequacy of the coronary circulation at a particular time. When positive, it indicates a diminished coronary reserve. It yields no information concerning the nature or extent of the pathologic lesions in the heart.

If the precautions outlined are observed, the anoxemia test is a simple, safe procedure. With the proper selection of patients, even the mildly unpleasant reactions can be largely avoided. It has been shown to be of clinical usefulness in the differential diagnosis of coronary insufficiency. It has been employed also to study the effects of various drugs on the coronary circulation of man.¹² It does not require active cooperation on the part of the patient and anoxemia can be abolished promptly at any time by administering 100 per cent oxygen.

For routine clinical purposes, the anoxemia test should be restricted to those patients in whom the diagnosis of coronary insufficiency is in doubt. Only a positive result is significant.

The following case history illustrates the manner in which the test may aid in diagnosis:

CASE 11. C. F., male, aged forty years, was an accountant. As a child, he had mild rheumatic pains in his knees and ankles which disappeared after tonsillectomy. He had never been seriously ill. He smoked thirty pipefuls daily and usually a cigar in the evening. He exercised spasmodically and never strenuously.

Two months before his first visit, he was awakened during the night by pain in the right shoulder which was gone by morning. A few days later, his car locked bumpers with another and an hour of vigorous exertion in cold weather was required to straighten out the damage. After this incident he noted pain in the right shoulder, right arm and right upper back when he walked rapidly. This gradually became less severe and was localized to the muscles in the upper portion of the arm. His physician suspected that the pain was cardiac in origin but did not test the effect of nitroglycerine.

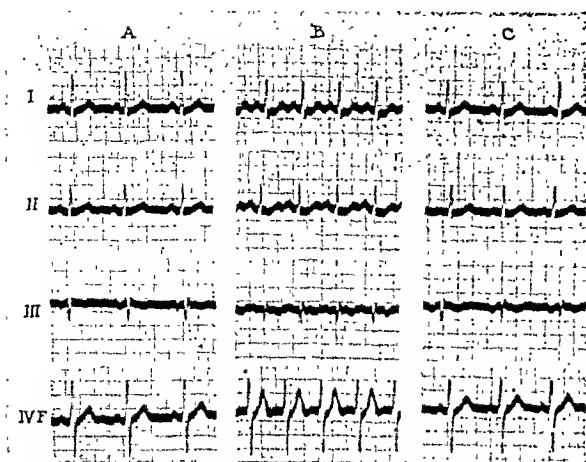


FIG. 3. Male, aged forty years, with pain in right shoulder upon effort. The clinical examination was negative. Anoxemia test indicates coronary insufficiency. A, control; B, after breathing 10 per cent oxygen for twenty minutes. The patient had slight pain in right shoulder after eighteen minutes. C, after breathing 100 per cent oxygen for two minutes; changes due to oxygen-want have disappeared.

On examination he appeared short and thick-set. There was no retinal sclerosis. The heart was not enlarged on percussion. The rhythm was regular; the rate was 76. The sounds were of moderate intensity and clear. The blood pressure was 126/76. Fluoroscopic examination and orthodiagraphic measurement showed the heart and aorta to be normal in size and shape. The electrocardiogram showed left axis deviation and a prominent Q wave was noted in lead III.

The results of the anoxemia test are shown in Figure 3. The control record, in which the rate was 76, has already been described. After breathing 10 per cent oxygen for twenty minutes, he became somewhat cyanotic and the heart rate rose to 116 per minute. The changes in the electrocardiogram indicating coronary insufficiency are quite evident. There is partial inversion of the T wave in leads I and II, with depression of the RS-T segment in these leads as well as in lead IVF. He stated that at the end of eighteen minutes he felt pain in the right shoulder similar to that experienced on exertion, although it was somewhat less intense, so that he did not signal that he wished the test to be stopped. The final record in the series shows the disappearance of the changes caused by induced anoxemia after breathing 100 per cent oxygen for two minutes and room air for one minute. The heart rate at this time was 82 per minute.

The patient was relatively young and the results of the usual examinations were negative. The symptoms were suggestive but not charac-

teristic of coronary insufficiency. The anoxemia test left no doubt as to the source of his discomfort.

THERAPEUTIC USE OF REST

It has become the fashion in recent years to disparage rest as a therapeutic measure in the management of cardiac patients.¹³ Prolonged recumbency, it is said, leads to the development of thrombosis in the veins of the leg and hence predisposes to pulmonary embolism. It favors the development of hypostatic pneumonia in the aged. It shifts edema fluid toward the lungs instead of letting it gravitate to the legs. It causes hemodilution and increased blood volume as a result of the flow of fluid from the tissue spaces into the blood stream.¹⁴ It has a bad psychologic effect for it encourages a state of cardiac invalidism. Finally, there is no good evidence, say these critics, that prolonged rest aids materially in promoting recovery.

It seems to the author that there has been too much criticism of the use of rest, particularly in the treatment of patients with coronary heart disease. There are many degrees of rest, ranging from complete inactivity in the recumbent position to merely the avoidance of athletic sports. There are different types of rest: physical, mental and emotional. So, too, there are numerous types of disorders caused by coronary heart disease and these, in turn, vary in severity. The age and psychologic make-up of the individual likewise play an important part in determining the physician's plan of management. With so many combinations possible, it is inconceivable that any standard regimen should best serve to accomplish the desired ends.

No one will deny that following severe, acute cardiac infarction, the patient should be kept quiet and in bed. The use of the commode instead of the bedpan, however, should be permitted early. There is no need to insist upon a flat bed after the stage of shock has passed; indeed, many patients who are not gravely ill prefer semirecumbency from the outset. Movements of the toes, feet and legs are encouraged; massage of the legs is given early and the position in

bed is changed frequently with the help of a nurse or orderly.

The circulation should be aided, whenever there are even slight signs of failure, by the administration of oxygen and the use of digitalis. We have proved to our own satisfaction that digitalis, given in the presence of an acute infarct, does not increase the likelihood of embolism, rupture of the heart or ventricular fibrillation. It accomplishes, in this condition, all that may be expected of it in a heart failing from other causes. It helps to abolish circulatory stasis.

The guidance of the patient during the periods of recovery and convalescence requires judgment and experience.¹⁵ No laboratory test, such as the sedimentation rate, and no electrocardiographic criteria can be used to the exclusion of the clinical picture as a whole. Often, a persistent elevation of the sedimentation rate causes anxiety; allowing the patient out of bed is sometimes followed by a drop to normal.

It is easier, perhaps, to point out the possible dangers of rest than to gauge its benefits. Following cardiac infarction, those who are given adequate rest during the early weeks and months fare best in the years to come. That is an observation which, to the author, has seemed clear but it cannot be readily substantiated by scientific proof. Certainly, many whose outlook has seemed poor, after long periods of inactivity and freedom from business cares, have made a remarkably good functional recovery.

The same is true in some patients with frequently recurring anginal pain, induced by relatively slight effort or occurring even without it. They need not necessarily go to bed but weeks or months of freedom from any but minimal exertion and absence from customary responsibilities appear to aid in the development of a collateral circulation which eventually is adequate for the performance of ordinary amounts of work. From the point of view of dollars and cents, such a period of inactivity often proves to be an investment which pays large dividends.

Rest, like a drug, is a form of therapy which exerts its maximal effectiveness in amounts which are neither too large nor too

small. There is a proper formula for each patient which must be adjusted to varying circumstances.

ACUTE, FATAL CORONARY INSUFFICIENCY

Disease of the coronary arteries is the lesion most frequently associated with sudden death. Occlusion, either thrombotic or atherosclerotic, is to be regarded as an episode in the course of sclerosis and is not essential for abrupt cessation of the heart beat.

In a series of 376 fatal cases of coronary sclerosis, with and without thrombosis, death was sudden in 14 per cent of the total number. But of the cases of sclerosis without thrombosis, death occurred in this manner in only 12 per cent whereas in the cases in which a thrombus was present, death was sudden in 33 per cent.² It appears that the occurrence of thrombosis almost triples the likelihood of a sudden end. This might be anticipated, for closure further seriously reduces the carrying capacity of vessels already impaired by narrowing and loss of elasticity.

That sudden occlusion of a coronary artery can cause the ventricles to fibrillate was demonstrated in animal experiments by Cohnheim¹⁶ some sixty-five years ago but the mechanism concerned in death from coronary heart disease has been recorded infrequently in man. In 1939, Smith¹⁷ collected four cases in which the electrocardiogram showed ventricular fibrillation and added one of his own. Since then, four others have been reported.¹⁸ In these nine cases, autopsies were performed in only three instances. In two other cases, total standstill of the heart followed ventricular tachycardia without the appearance of ventricular fibrillation as an intermediate arrhythmia.¹⁹

It has been unusual then to record electrocardiographically the mechanism of the dying heart and to correlate the clinical picture with the autopsy findings. For this reason, the tenth proved instance of death due to ventricular fibrillation in a patient with coronary heart disease is here briefly presented. In this case, a tracing was obtained of the dying heart and a post mortem examination was made.

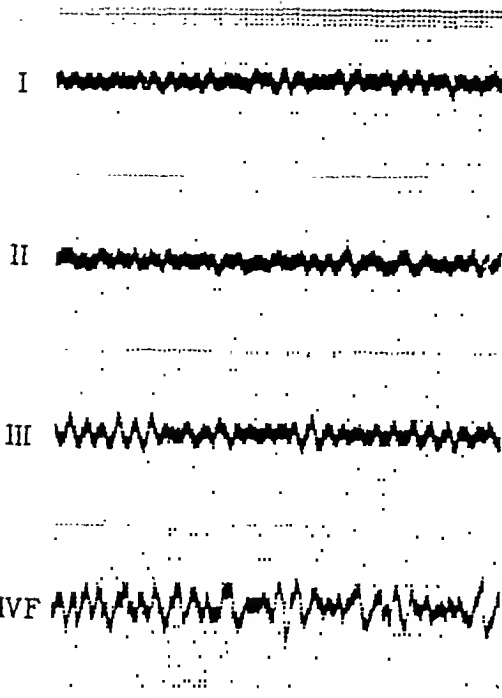


FIG. 4. Male, aged fifty-seven years. Sudden death occurred three hours after first symptoms of coronary thrombosis. Electrocardiogram shows ventricular fibrillation. Patient ceased breathing less than one minute after record was taken. At autopsy a fresh thrombus occluded the right coronary artery but there was no necrosis of the myocardium.

CASE III. G. A., an Italian born male, was fifty-seven years old at the time of his death. Nine years previously, a partial thyroidectomy was performed for diffuse toxic goiter, auricular fibrillation and cardiac insufficiency. It was noted then that his heart was enlarged. Following the operation, sinus rhythm was restored and the functional capacity of the heart was greatly improved. For economic reasons he resumed his work as a furniture mover and later was engaged by the city water department to dig trenches. He carried on this physical labor without discomfort.

On the morning of his death, he suddenly felt precordial and epigastric pressure which was not severe. When seen in the emergency room at the hospital, there were no signs of shock or of cardiac failure. The blood pressure was 136/96. The cardiac rate was 76; the rhythm was regular. A soft systolic murmur was heard at the apex. He was admitted to the overnight ward for observation and three hours after the onset of discomfort an electrocardiogram was taken. This showed ventricular fibrillation. (Fig. 4.) Less than one minute after the record was completed, he suddenly stopped breathing.

At autopsy the heart was found to be enlarged;

it weighed 510 Gm. Both coronary arteries contained numerous small atherosclerotic plaques. The right coronary artery, 6 cm. below its origin and about in the middle of its course, was obliterated by a greyish thrombus which was firmly attached to the wall of the vessel. The myocardium of the right ventricle was pale but no gross necrosis was seen.

Microscopic examination of the heart muscle showed hypertrophy of the fibers and a moderate increase in interstitial tissue. There was marked intimal thickening of several of the coronary arteries. No evidence of necrosis was found in either ventricle. Most of the viscera showed congestion but no other significant changes.

In this case, sudden death due to ventricular fibrillation occurred three hours after the onset of symptoms of coronary thrombosis. Occlusion of the coronary artery apparently was so recent that no softening of the heart muscle had occurred. Acute coronary insufficiency induced the arrhythmia which caused death.

SUMMARY

Some of the clinical features of coronary insufficiency have been given brief consideration. A classification of the common types has been presented for the purpose of correlating diverse manifestations, all of which are caused by an inadequate coronary blood flow. The importance of recognizing infarction has been stressed. It has been demonstrated that atherosclerotic changes in the coronary arteries often progress insidiously and that, in many instances, processes of repair compensate adequately for the damages of disease. Some of the cardinal points in diagnosis have been discussed. Too little attention has been given to cardiac enlargement alone which, in the absence of hypertension, valvular deformity or other obvious causes, affords presumptive evidence of coronary heart disease. The use and limitations of the anoxemia test as an aid in the recognition of coronary insufficiency have been described.

Because prolonged rest in bed has been credited with certain undesirable effects on the circulation, the impression apparently has been created that the importance of rest, in general, in the treatment of cardiac ailments has been overemphasized. In the

author's opinion, there has been too much criticism of the use of rest. It is the most valuable single therapeutic procedure in the management of the patient with coronary heart disease. The fault lies not in the remedy but in lack of discrimination in its application.

Acute coronary insufficiency is the most common cause of sudden death. In the few cases of coronary disease in which the mechanism of the dying heart has been recorded, ventricular fibrillation usually has occurred just before respiration ceased. Less frequently, ventricular tachycardia has been followed by total cardiac standstill.

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Experimental Renal Hypertension

HARRY GOLDBLATT, M.D.*

Los Angeles, California

DURING the period in which any medical subject is actively investigated it becomes necessary from time to time to summarize what has been accomplished. This has been done on the subject of hypertension in several books and reviews¹⁻¹¹ and much of this writing has been, of necessity, repetitious. This symposium, of which this discussion is merely the introduction, will also include much repetitious material, but it is written because it is hoped that it will reach many readers to whom previous publications have not been accessible and because it will include some new material. Few references will be given because extensive bibliographies are available in previous publications.¹⁻¹¹

It has now become customary to assign to Richard Bright the credit for the basic idea that hypertension may frequently be of renal origin. This has been done despite the full realization that Richard Bright never determined blood pressure in man and never proved that a state of hypertension actually existed. Certainly, he knew nothing of what is now termed essential hypertension. He did recognize, however, that the large, heavy heart found at autopsy in some patients, for which there was no other obvious explanation, was frequently associated with some abnormality of the kidneys. Bright related the increased weight of the heart to the disease of the kidneys in these patients and even suggested that a chemical substance in the blood, of renal origin, might have been the direct cause of the hypertrophy. He specu-

lated that this was in all likelihood due to increased action of the heart and increased resistance to the onflow of blood brought about by a hypothetical chemical substance. The latter idea is certainly in keeping with the modern concept that increased peripheral vascular resistance is, under most circumstances, the basic mechanism of elevated blood pressure.

Although Richard Bright may be credited with lighting the torch, credit should also be given to those who kept it alight. Chief among those who kept the idea of the possible renal origin of some forms of human hypertension alive was Volhard^{12,13} who believed that, at least in pale (malignant) hypertension, disease of the kidney played the important primary part in the pathogenesis of the elevated blood pressure. He searched for but failed to find a vasoconstrictor substance in the blood of patients in the malignant phase of essential hypertension. There are those who still deny that the kidneys ever play a primary part in the pathogenesis of hypertension, but it is now quite generally recognized that primary renal disease may be associated with human hypertension and that a causative relationship between the two conditions may exist. Few fail to accept the renal origin of hypertension associated with glomerulonephritis (acute and chronic), bilateral chronic pyelonephritis, bilateral polycystic disease of the kidneys, bilateral ureteral obstruction, renal amyloidosis and other conditions that involve considerable reduction of renal parenchyma. The existence of renal disease in such cases is

* From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif., and the Department of Pathology, University of Southern California.

usually determined by the accompanying abnormality of renal excretory function which is the direct result of the renal disease.

It is in the case of so-called essential hypertension that the primary renal origin of the elevated blood pressure is still held in doubt. In fact, essential hypertension by definition has been characterized as elevated blood pressure of unknown origin without recognizable disturbance of renal excretory function. A critical statistical analysis of the data on renal excretory function in patients with essential hypertension by Dalton and Newsom led them to conclude that some impairment of the ability to concentrate urine and to excrete phenolsulphonphthalein is always detectable. The fact that in the early stages of essential hypertension, and even for many years after the onset, renal excretory functional abnormality cannot be demonstrated and that it is often absent throughout the entire course of the disease, has convinced some investigators that most cases of essential hypertension are not on a renal basis. The arguments usually adduced against the renal origin of essential hypertension include the occasional failure to find at autopsy any significant intrarenal vascular disease or any other abnormality of renal tissue.

After the existence of elevated blood pressure in man had been discovered the fact that hypertension was the cause of the enlarged heavy hearts observed by Bright was fully realized. Although increased action of the heart has been established as a condition which exists in the state of hypertension, it is now generally regarded as secondary to the hypertension produced by increased peripheral vascular resistance. Increased volume of the blood, although it occurs in the state of plethora which may be associated with hypertension, has certainly been eliminated as the cause of hypertension in general and has not been found to exist in essential hypertension. The same holds true for increased viscosity of the blood which has been excluded as the primary cause of elevated blood pressure. The impor-

tant problem that remains is the elucidation of the pathogenesis of increased peripheral vascular resistance which is now recognized as the determinant of the elevated blood pressure and for which there can be at least two explanations. The more obvious cause would seem to be the widespread organic disease of small arteries and arterioles, discovered by Johnson and by Gull and Sutton, which could be a mechanical cause of the increased peripheral resistance; but this view has never been supported by the demonstration of organic vascular disease so widespread as to determine a mechanical increase of peripheral vascular resistance. The other and more probable mechanism of increased peripheral vascular resistance could be peripheral vasospasm induced by a nervous or humoral (including endocrine) mechanism. The studies of Prinzmetal¹⁴ and of Pickering¹⁵ minimize the possible primary importance of neurogenic vasospasm and no convincing evidence has been adduced for endocrinogenic vasospasm as the general primary cause of essential hypertension. This does not exclude recognition of the existence of patients with hypertension resulting from psychoneurogenic stimuli, diminution of the sensitivity of the carotid sinuses, hyperepinephrinemia or abnormal pituitary function. Our own observations led us to experimental investigation of the possible renal origin of peripheral vasospasm.

EXPERIMENTAL PRODUCTION OF RENAL HYPERTENSION

Most of the experimental work on the production of hypertension that was done prior to 1928, with the idea that hypertension might be of renal origin, chiefly involved methods which were likely also to produce disturbance of renal excretory function. Among these were unilateral and bilateral nephrectomy, reduction of the amount of functioning renal tissue by resection, the effect of a nephrotoxic substance, irradiation with roentgen rays, occlusion of one or both ureters, acute compression of the kidneys, embolism, passive hyperemia due to constriction of the main renal vein,

permanent occlusion of the main renal artery, vein and ureter of both kidneys, arteriovenous anastomosis and occlusion of the main renal arteries. A few of these methods were followed by some elevation of blood pressure but in most of the experiments hypertension did not persist and, in most cases, there was no elevation of blood pressure, or the hypertension was fleeting and probably of nervous reflex origin. Contradictory results were obtained by different investigators using the same methods. None of the methods actually reproduced the anatomic or even the physiologic state of the kidneys in benign essential hypertension. If the hypertension persisted for any length of time, it was usually accompanied by renal excretory impairment with or without uremia.

The idea of producing hypertension by a disturbance of intrarenal hemodynamics was based primarily upon the observation, well known to pathologists, that intrarenal stenosing arterial and arteriolar sclerosis is found with great frequency in both the benign and malignant phases of essential hypertension. It was considered that the part possibly played by such a disturbance of intrarenal hemodynamics should be susceptible of experimental investigation. The most important of the working hypotheses of this study were: (1) If stenosing vascular disease limited to the kidneys, or any renal condition which produces the same effect on renal circulation, be the primary factor in the initiation of most cases of essential hypertension, then reproduction of the counterpart of the physiologic effects of such vascular disease, no matter how it might be accomplished, should result in the development of hypertension; (2) renal excretory functional disturbance should not be a necessary accompaniment of this type of experimental hypertension and (3) the probable disturbance of renal hemodynamics produced by intrarenal stenosing vascular disease might be reproduced by constriction of the main renal artery and, if the basic hypothesis be correct, should result in the development of elevated blood pressure.

It was considered that fulfillment of all these conditions would answer the requirements of the definition of essential hypertension and signify the experimental reproduction of so-called essential hypertension.

It is granted that the best procedure would have been to reproduce the intrarenal anatomic abnormality, namely, arterial and arteriolar sclerosis localized to the kidneys, but there was no known way of doing this at the time and it has not yet been accomplished. Since the main effects of intrarenal arterial and arteriolar disease of the kidney are probably reduction of intraglomerular capillary pressure and alteration, possibly reduction, of blood flow to the functioning components of the kidney, it was considered that these two effects, and any other physiologic disturbances that might occur, might be produced by the permanent constriction (not occlusion) of the main renal artery by means of a clamp. It should be appreciated at once that the method decided upon was a compromise, that it does not mean that stenosing arteriosclerosis of the main renal artery was considered to be a frequent finding in cases of human essential hypertension, or that application of the clamp was considered to reproduce exactly the anatomical state of the kidney in essential hypertension. This incorrect interpretation has been made by a number of authors and investigators.

Details about the clamp and about the instruments used for its application have been given in previous publications¹⁶ and as a result will be omitted from this discussion. The principal effects of the application of the clamp on the main renal artery will be merely summarized herein.

Effect of Constriction of One Main Renal Artery. It was soon found, and unexpectedly, that constriction of the main renal artery of only one kidney was sufficient to induce a rise of blood pressure within twenty-four to seventy-two hours after the application of the clamp. In the dog, the elevated blood pressure usually lasts from four to six weeks and, only exceptionally, for several months. The maximum rise is

usually reached in about one week and the blood pressure remains elevated at that level for another week, after which it gradually returns to normal. In the sheep, the goat and the rat, the elevation of blood pressure as a result of unilateral constriction of the main renal artery may last much longer than in the dog. In all these animals, removal of the one kidney with the main renal artery constricted results in a prompt return of the blood pressure to normal. These findings drew attention to the possibility that even human hypertension might be on a unilateral renal basis and the later finding that, in man also, removal of the one diseased kidney results in a return of the blood pressure to normal in those patients in whom the other kidney is normal.

Effect of Constriction of Both Main Renal Arteries. Constriction of both main renal arteries, either at the same time or after an interval, results in permanent elevation of the blood pressure. The same effect is produced by constriction of one main renal artery and contralateral nephrectomy. By this means persistent hypertension has been produced in the dog, monkey, rabbit, rat, cat, sheep and goat and the blood pressure has remained elevated in some dogs for more than six years. Cash and Wood¹⁷ and we have shown that this is true hypertension because both systolic and diastolic pressures become elevated. In some of the animals, even when both renal arteries are constricted, the blood pressure tends to return to a lower level in several months, and increased constriction of the renal arteries is necessary to re-elevate the blood pressure which then often remains elevated for years.

Perhaps the most important finding, other than the elevation of blood pressure, was that in animals with persistent hypertension due to moderate constriction of both main renal arteries there was no significant alteration of renal excretory function. Mere disturbance of intrarenal hemodynamics, therefore, is sufficient to produce hypertension without disturbance of renal excretory function. Thus, the two most important of the working hypotheses of these experi-

ments are satisfied. Although the direct application of these observations to man is perhaps not justifiable, yet these results do offer experimental evidence for the view that benign essential human hypertension, usually associated with intrarenal arterio- and arteriolosclerosis without impairment of renal excretory function, may also be of renal origin. Much evidence, to be summarized later, has accumulated in favor of this view.

As control observations, it has been shown that constriction of the splenic arteries, of both femoral arteries and even of the aorta below the origin of both main renal arteries is not followed by elevation of blood pressure. Constriction of the aorta above the origin of both main renal arteries does result in significant elevation of the blood pressure but this is evidently due to disturbance of the circulation to the kidneys.

There have been some attempts to minimize the importance of these experiments because the main renal artery in human hypertension is not commonly stenotic. This is admitted, of course, but it does not constitute a good reason why experimental constriction of the main renal artery should not be considered capable of reproducing the functional state of the human kidney in essential hypertension. Although Yuile¹⁸ and Blackman¹⁹ have actually drawn attention to the not infrequent existence of stenosing arteriosclerosis of one or both main renal arteries in association with human hypertension, it is important to emphasize that constriction of the main renal artery was an expedient resorted to experimentally because it was the only method that seemed likely to produce a circulatory disturbance of the kidney resembling the most probable effect of *intrarenal* stenosing arterial and arteriolar sclerosis. To regard the experimental type of hypertension as not exactly like human essential hypertension because the main renal artery of human beings with hypertension is not frequently stenotic, is to misunderstand the whole problem and the main purpose of the experimental procedures

which were used for the production of experimental renal hypertension. Recognition of the probable similarity of these two processes is necessary for proper understanding and evaluation of the contributions made by the great variety of studies carried out on animals with experimental renal hypertension.

It is well known that in some cases of human essential hypertension the fatal outcome is associated with and due to renal excretory failure. In some instances the renal excretory insufficiency is an initial accompaniment of the hypertension and the condition proves rapidly fatal with death from uræmia. It is interesting that this condition may be reproduced at will in animals. If both main renal arteries are greatly constricted from the start or if moderate constriction is practiced at first and great constriction later, hypertension accompanied by variable degrees of impairment of renal excretory function results. This same effect can be produced by excessive constriction of one main renal artery with contralateral nephrectomy or contralateral ureteral occlusion. In those animals that develop great impairment of renal excretory function along with hypertension, fatal convulsive uræmia occurs and, at autopsy, the small arteries and arterioles in many organs show pathologic changes which resemble those observed in the malignant phase of essential hypertension.

Thus, hypertensive states resembling both benign and malignant phases of essential hypertension have been produced experimentally in animals merely by varying the degree of constriction of the main renal arteries, with consequent alteration in the intrarenal hemodynamics, the exact nature of which has not yet been determined. The evidence that has accumulated to indicate that the benign and malignant phases of human essential hypertension may also be primarily of renal origin will be summarized in a latter part of this paper.

In some animals in which examination of the kidneys shows that the potential accessory circulation to the periphery of the

kidney has become strikingly prominent, with large arterial vessels entering the cortex of the kidney from the various surrounding organs and structures, it has been demonstrated that decapsulation of the kidney and enclosure of one or both kidneys in a fish-skin condom frequently results in a relevation of the blood pressure which persists. This type of membrane does not induce the development of a thick hull of connective tissue around the kidney (such as is induced by wrapping cellophane, collodion or silk around a kidney) but it does reduce the accessory circulation to the kidney and it is thought that this induces the relevation of blood pressure. Cellophane, collodion and silk membranes (as employed by Page and others) have been wrapped around kidneys and elevation of blood pressure has been observed to develop weeks or months after the application of these membranes. The elevation of blood pressure in these animals has been considered to be due to perinephritis and the compression of the renal substance by the thick hull of connective tissue which develops around the kidneys. There is no proof that actual compression of the kidney occurs in these circumstances. In fact, there is no proof that the mechanism of the elevated blood pressure is not due to the scar tissue which also develops around the renal pedicle, with possible constriction of the renal artery, vein and even ureter of the kidney. Two indications of the possibility of these effects are the passive hyperemia (venous obstruction) and the hydronephrosis (ureteral obstruction) which, in some degree, are almost invariably observed at autopsy in such kidneys. More work should be done on this type of hypertension to settle this question. It is considered that the pathogenesis of the hypertension, even that resulting from application of a membrane, is similar to the hypertension which results from constriction of the main renal arteries. The one important drawback of the method is that impairment of renal function is an almost invariable accompaniment of the hypertension and that fatal

uremia (the malignant phase) is a common outcome.

Pathologic Changes in the Tissues of Animals with Experimental Renal Hypertension. The intrarenal pathologic changes which result from constriction of the main renal artery are directly dependent upon the degree of constriction of this vessel. In animals in the benign phase of hypertension produced by moderate constriction of the main renal arteries without accompanying renal excretory disturbance, the kidneys may show little if any gross or microscopic abnormalities. In the early period after constriction, variable degrees of cloudy swelling and even changes in the mitochondria of the lining epithelium of the tubules, especially of the proximal convoluted tubules, may be found although later no obvious anatomic changes are detectable. Pathologic changes in the anatomic structure of the kidneys are therefore not necessary for the production of the elevated blood pressure. As Selkurt²⁰ has shown, striking physiologic signs of tubular damage may sometimes occur without correspondingly striking histologic alterations in the kidney as a result of variable degrees of anoxia for variable periods of time. This must depend upon intracellular changes which are not detectable by the usual methods.

In some animals, even in the benign phase after several months, one kidney may be found atrophic although in the interval there was no significant disturbance of total renal excretory function. In such animals the other kidney is usually hypertrophic and both in gross and microscopic examination appears normal. In the malignant phase, advanced parenchymatous degeneration and even diffuse necrosis, with or without hemorrhage, may occur in one or both kidneys.

Even after six years of persistent benign hypertension in dogs, no significant pathologic changes have been observed in the intima of the aorta or of large or small arteries that can be considered a direct consequence of hypertension. Slight to moderate hypertrophy of the heart has been

observed, and thickening of the media of the large and small arteries due to hypertrophy and hyperplasia of the muscle fibers also occurs but intimal sclerosis has not been observed. The results of the experiments on the benign phase of hypertension in animals has therefore afforded no proof for the view that hypertension by itself is a sufficient condition for the production of generalized, true, simple, intimal arterial or arteriolar sclerosis.

In dogs, monkeys, rabbits, rats, sheep and goats that have died in the malignant phase of hypertension, even when terminating fatally in as little as forty-eight to seventy-two hours, profound changes in the blood vessels have been observed. These changes are similar in all respects to those seen in the terminal phase of human malignant hypertension but are not to be confused with arteriosclerosis. The gross manifestation consists mainly of petechiae throughout the gastrointestinal tract, in the gall-bladder, the urinary bladder, pancreas, adrenals, brain, pericardium and myocardium. Similar lesions have also been observed in the adventitia of the aorta and of some of the larger arteries. Microscopically, the small arteries and arterioles are the seat of necrosis and fibrinoid degeneration, with or without vascular and perivascular inflammation characterized by exudation of polymorphonuclear leukocytes and some lymphoid cells. The necrotizing and inflammatory changes in the arterioles are identical with those observed in the terminal phase of malignant hypertension. These lesions have not been observed in the blood vessels of kidneys with a constricted main renal artery; but when one main renal artery is greatly constricted and the ureter of the other kidney is ligated, arteriolar lesions of the malignant phase may develop in the kidney with the occluded ureter in which intrarenal arterial tension was probably increased. It is considered, therefore, that the development of these necrotizing arteriolar lesions and especially of the petechiae, many of which are undoubtedly of capillary origin, requires

both the action of some chemical substance and the factor of increased tension. The pathogenesis of the arteriolar necrosis has been discussed in several previous publications but is still the subject of controversy. There are those who believe that hypertension *per se* is a sufficient condition for the production of these lesions but the unequivocal proof for this contention is still wanting. That elevated intravascular pressure alone is not a sufficient condition for the production of necrotizing arteriolar lesions is indicated by the fact that they are absent from the organs of dogs that for many years have had pronounced hypertension without accompanying disturbance of renal excretory function. This lesion has never been reported (and we have never observed it) in animals with experimental neurogenic hypertension of long-standing. This would certainly indicate that intense vasospasm alone is not a determinant of these lesions. Bilaterally nephrectomized animals with profound azotemia but without hypertension do not develop necrotizing lesions of the arterioles and associated petechiae. This indicates that the chemical factor alone is not sufficient for the production of the arteriolar lesions. That the lesions of the arterioles are not those of ischemic necrosis is shown by their absence from the ischemic kidneys of the animals and their presence in organs in which there is no obvious ischemia. The exact nature of the chemical substance or substances which play the important part in the production of the anatomic lesions has not yet been elucidated. Winternitz and collaborators²¹ have been able to produce lesions of a similar nature by repeated injections of an extract of kidneys, but this does not prove that these chemical substances by themselves have the ability to produce these lesions and there is certainly no proof that the renin which was present in these extracts was the chemical substance responsible for the lesions. The vasculitis and perivasculitis are probably a reaction to the degeneration and necrosis of the walls of the arterioles or may be caused by the same agent that

produces the necrosis. Lesions of arterioles similar to those of the malignant phase have been produced by the repeated intravenous injections of tyramine but this does not justify the inference that tyramine is responsible for the lesions of the malignant phase.

Malignant arteriolar lesions have been observed by Wilson and Byrom²² and others in the contralateral kidney of rats with hypertension caused by constriction of one main renal artery. We have not been able to confirm these observations in dogs, rabbits, monkeys, sheep or goats with hypertension due to constriction of one main renal artery. That hypertension by itself is able to cause the characteristic malignant arteriolar lesions in an animal with hypertension due to constriction of one main renal artery has therefore not been substantiated in experiments on other animals. All the glomerular and interstitial inflammatory lesions, as well as the vascular lesions within an otherwise supposedly normal rat kidney, have been observed by us in the kidneys of rats with normal blood pressure. A possible explanation of the changes in the arterioles of the contralateral kidney observed by Wilson and Byrom and the others may be the fact that they were unaware of the frequent coexistence of hydronephrosis or pyelonephritis in one or both kidneys of adult rats. By constriction of only one main renal artery they may have been dealing, in some of these rats, with bilateral renal disease. There is, of course, the remaining possibility that the rat differs in this respect from all other animals.

Changes in Organs Other than the Kidney in Experimental Renal Hypertension. In experimental renal hypertension the pulse rate remains unaltered and there is no significant alteration in the output of blood from the heart. The blood volume in hypertensive dogs shows no significant alteration from the normal. The blood pressure in the lesser circulation (main pulmonary artery) is also within the limits of normal, indicating that the pulmonic vessels are not affected by peripheral vascular constriction. No signifi-

changes have been observed in the blood, with the exception of retention of nitrogenous products in the malignant phase. The pH of the blood remains normal in animals in the benign phase of hypertension. The lipid and protein content of the plasma shows no alterations but a slight increase of free cholesterol at the expense of the esterified fraction has been reported by Page. To this he has attached no special significance.

Animals in the malignant phase with retention of nitrogenous products also show retention of guanidine compounds, but no special significance has been attached to this pressor substance in the blood because it does not accumulate in the blood in the benign phase. A redistribution of the water content of skeletal muscles of dogs with experimental renal hypertension has been reported. This occurs mostly in the malignant phase and merely indicates some extracellular edema.

It is of interest that excision of the carotid sinus and of the cardiaortic nerves does not effect a lowering of the blood pressure in animals with constriction of the main renal arteries. We have found that excision of both carotid sinuses did not alter the development of hypertension produced by renal ischemia and that the level of blood pressure reached by such animals was no different from that of animals with intact carotid sinuses. It would seem that the regulatory system of the blood pressure functions actively in experimental renal hypertension and that it probably acts normally although at a high level. It has been found that animals with experimental renal hypertension react in hypersensitive fashion to injections of adrenalin, tyramine and pitressin, but no one has suggested that these substances play any part in the origin of the elevated blood pressure. On the contrary, Robbers and Westenhoffer²³ have concluded that tyramine cannot be the cause of experimental renal hypertension because they found that injection of cocaine causes no fall of blood pressure in hypertensive dogs. The dog's reaction to the cold

pressor test has been found to be the same after the development of hypertension as in the prehypertensive state.

An interesting observation, confirmed by many investigators, is the fall of blood pressure in the hypertensive dog in the presence of an infection, especially distemper, with a return of the blood pressure to the initial level after the infection disappears. The slow return of the blood pressure to normal in the case of distemper is probably due to the slow recovery of the animals from this infection. Similar effects can be obtained by the injection of bacterial products, for example, typhoid vaccine injected intravenously. Whether this effect is produced by the dilatation of systemic arterioles and decrease of peripheral resistance, or by dilatation of afferent glomerular arterioles and increase of intraglomerular pressure, has not been established.

Pathogenesis of Experimental Renal Hypertension. As soon as the successful production of experimental renal hypertension had been accomplished, it was realized that this might afford an opportunity to determine the possible causal relationship between hypertension and the arterio- and arteriosclerosis so frequently observed in association with hypertension in man.

The arteriolar sclerosis of the kidneys which has been reported by Fishberg,²⁴ Bell and Clawson²⁵ Moritz and Oldt²⁶ and others to be an almost constant necropsy finding in cases of human essential hypertension, has been interpreted by some as proof for the view that the hypertension comes first and that it is the cause of the renal vascular disease. Biopsy specimens of kidney obtained from the same individuals before and after the development of hypertension would, of course, help to solve this problem. There is no way of determining which persons will develop hypertension, and, for many other reasons, such a study of human beings is not possible. Biopsy specimens of kidneys in cases of established human hypertension have, however, been obtained by Castleman and Smithwick.²⁷ Their study did not lead to a solution of the problem and there is

certainly no good reason for accepting the conclusion of the authors that the results of their investigation show that the vascular disease is caused by or develops after hypertension. Study of a few arterioles in a minute specimen from the periphery of the cortex of the kidney can hardly afford any estimate of the hemodynamic state of the entire kidney. As a matter of fact, stenosis of one, large intrarenal artery could easily account for profound hemodynamic disturbances in a large mass of kidney substance supplied by thousands of arterioles that are not themselves diseased. Such intrarenal stenosing arteriosclerosis of large intrarenal vessels is a common finding in kidneys with vascular disease. It is the opinion of the author that the possible contribution of this obliterative sclerosis of the large intrarenal arteries, and even of the main extrarenal artery, to the disturbance of intrarenal hemodynamics has been underestimated. That extrarenal obliterative arteriosclerosis of the main renal artery can and frequently does occur in individuals with hypertension has been shown by Blackman.¹⁹ This may or may not be accompanied by intrarenal arterial and arteriolar sclerosis. At no time has it been asserted by us that stenosis of the main renal artery, unilateral or bilateral, is a common cause of human essential hypertension or that experimental constriction of the main renal artery reproduces the anatomic state of the vascular system in the hypertensive kidney. However, when it exists, the part played by such obliterative sclerosis of the main renal artery cannot be denied and the effect of the clamp is regarded as reproducing the intrarenal hemodynamic disturbance of the kidney produced by the *intrarenal* arterial and arteriolar sclerosis, the condition commonly found in the kidney of patients with hypertension.

Production of the counterpart of the benign and malignant phases of human hypertension in animals has made possible investigation of the probable pathogenesis of hypertension in man. The following mechanisms may be involved in elevation of blood pressure: (1) neurogenic, with vaso-

constriction due to afferent nervous stimuli from the nerve endings in the kidneys to the vasomotor centers or sympathetic ganglia; (2) afferent stimuli from the kidneys, with resulting output of an increased amount of some known internal secretion which produces vasoconstriction either by central or peripheral action; (3) the entrance into the circulation of a primary pressor substance of renal origin, or the formation of a pressor substance as the result of interaction of a renal substance with a substance or substances already present in the blood.

Neurogenic Mechanism. By elimination of various portions of the nervous system and constriction of the main renal arteries before or after the section or excision of the nerves, it was shown that experimental renal hypertension is not caused by a nervous reflex from the kidney affecting the vasomotor mechanism of the body. Since a nervous reflex originating in the kidney is not the cause of experimental renal hypertension, a humoral mechanism is probably at play. There are those however who, like Ogden,²⁸ concede that a renal humoral pressor mechanism initiates experimental renal hypertension but believe that this is later superseded by a neurogenic mechanism mediated through the sympathetic nervous system. This view has not yet been established but it deserves more investigation.

Endocrinogenic Mechanism. No one denies the existence of human hypertension of endocrine origin. Hypertension associated with pheochromocytoma of the adrenal and with pituitary basophilic adenoma or basophilism are cases of this kind. However, there is certainly no good reason for believing that essential human hypertension is of endocrine origin. In the case of experimental renal hypertension, it has been shown that hypophysectomy, thyroidectomy, gonadectomy and pancreatectomy have no significant effect in preventing or lowering experimental renal hypertension in the dog. It has also been shown that the only endocrine organ which may possibly play a significant, even if only a secondary part in experimental renal hypertension, is the

adrenal gland. The medulla of the adrenal plays no part in the origin or maintenance of the elevated blood pressure in experimental renal hypertension, but there is some indication that the adrenal cortex may be of secondary importance. Complete excision of both adrenals in the dog interferes with the development of hypertension due to constriction of the main renal arteries unless adequate supportive and substitution therapy is given. When only a small part of the cortex of a single adrenal remains, there is no interference with the development of experimental renal hypertension in the dog. If both adrenals of a hypertensive animal are removed, the blood pressure promptly falls to normal. There is some evidence that the mode of action of the cortical hormone is to influence the production of a pseudoglobulin in the blood which acts as a substrate for the activity of renin to form the pressor substance, hypertensin.

The production of hypertension in dogs²⁹ by ligation of the hilar adrenal vein and the grossly visible small arteries and veins at either the superior or inferior pole of only one adrenal (Victor²⁹) has not been confirmed by those who have repeated this experiment. The significance of this contribution remains to be established.

The recent contributions of Selye to the subject of the hormonal factors in hypertension, including the so-called *endocrine kidney*, await confirmation and will not be discussed in detail in this paper.

Renal Humoral Mechanism. That a humoral mechanism might be responsible for the elevated blood pressure in experimental renal hypertension was first indicated by the effect of tying off the renal veins in dogs with the main renal arteries constricted adequately to produce hypertension. Although these animals developed uremia and died in two to seven days, at no time did they show any elevation of blood pressure. The gradual elimination of a possible primary part played by the nervous and endocrine systems also stimulated the search for a probable humoral mechanism of renal origin which might be responsible for the

elevation of the blood pressure in this type of hypertension and possibly also in human essential hypertension associated with renal disease. Most of the recent contributions to this subject have dealt with the humoral mechanism, about which there are now two separate and distinct views: (1) that a kidney with a constricted main renal artery, or with any other pathologic condition which may bring about a similar disturbance of renal circulation, may be the source of a chemical substance which when it enters the circulation raises the blood pressure; (2) that the normal kidney is ordinarily the source of a substance which has the ability to prevent hypertension and that it is the absence, destruction or neutralization of this substance which results in elevated blood pressure (Grollman). Most of the evidence presented to date favors the former view but unequivocal proof for this view is still lacking.

The fact that interference with the blood supply to any other organ but the kidney does not result in either temporary or permanent elevation of the blood pressure and that constriction of the celiac axis, the superior mesenteric artery, the femoral and splenic arteries and even the aorta below both main renal arteries fails to raise the blood pressure can be adduced as evidence that the kidney is unique in this effect. It has been shown that azotemia alone is not a sufficient condition for the elevation of blood pressure because bilateral nephrectomy or anastomosis between renal artery and vein, although followed by profound azotemia, are not followed by the development of hypertension. Acute nephrosis with uremia due to various metallic poisons also rarely results in an elevation of blood pressure. The shunting of the venous blood of a unilaterally nephrectomized dog from its only kidney through the liver by means of a reversed Eck-fistula does not prevent the development of hypertension due to constriction of the main renal artery, nor does it lower the blood pressure in a hypertensive animal. This excludes any

important effect of the liver on the pressor substance of renal origin.

Direct demonstration of the probable existence of a humoral mechanism of experimental renal hypertension was given by the transplantation of a kidney to the neck or groin of a bilaterally nephrectomized dog or rabbit (Braun-Menendez and collaborators). When the renal artery of the transplanted kidney, with no nervous connection with the rest of the body, was constricted, a pressor effect resulted after the usual interval. Also, transplantation of a partially or completely ischemic kidney from one dog to the neck of a bilaterally nephrectomized dog resulted in an immediate temporary elevation of the blood pressure when the circulation to the ischemic kidney was restored. This indicated that some chemical substance capable of bringing about peripheral vasoconstriction had been released from the ischemic kidney into the circulation. Whether or not this substance in the kidney is itself a vasoconstrictor or whether it becomes a vasoconstrictor after entering the blood stream is not elucidated by this experiment. Demonstration that sudden release of a clamp kept for five to seven hours on the entire renal pedicle (artery, vein and ureter) was followed by a prompt elevation of the blood pressure is another indication of the existence of a humoral mechanism. Removal of a completely ischemic kidney from the body without release of the clamp on the pedicle and perfusion of the kidney with normal saline solution resulted in the demonstration of a powerful pressor substance in the perfusate when injected into the same or into another animal (Prinzmetal, Lewis and Leo).³⁰ It is now generally recognized that the chemical substances involved in all of these experiments are probably the same.

By use of the Löwen-Trendelenburg technique in the South American toad the presence of a vasoconstrictor substance in the blood plasma obtained from the renal vein of a dog with experimental renal hypertension due to complete constriction

of the main renal artery was demonstrated. Most investigators failed to find pressor substances in the systemic blood of hypertensive dogs or of human beings with hypertension. There was also no effect of blood from hypertensive dogs on the tonus of surviving arterial rings (Wakerlin), but Solandt and collaborators³¹ did observe a definite rise in the blood pressure of a bilaterally nephrectomized dog to which they gave a direct transfusion of blood from a hypertensive dog; and Braun-Menendez and Fasciolo observed a pressor effect in a normal dog as a result of the intravenous injection of 100 cc. of renal venous blood from the transplanted renal ischemic kidney of another dog.

Piperidomethyl-benzodioxane (933F) does not have greater effect on the blood pressure of a hypertensive animal than on that of a normal one, whereas in both normal and hypertensive animals, the effect of epinephrine is completely reversed by an injection of this substance. This indicates that the effective vasoconstrictor substance of the kidney is not sympathomimetic.

All of the investigations mentioned above pointed to a chemical agent of renal origin as the probable cause of the elevated blood pressure in experimental renal hypertension. The search for the hypothetical pressor agent began with the repetition of some old experiments made by Tigerstedt and Bergman³² which had been confirmed by some and denied by others. They consisted of the demonstration of a substance in the crude saline extract of a normal rabbit kidney which was capable of inducing a pressor effect when injected intravenously into a normal rabbit. For this substance the original term, renin, suggested by these authors has now been accepted as the name of the basic principle of the humoral mechanism of experimental renal hypertension. The demonstration by Prinzmetal and others of the existence of a greater amount of this substance in the kidneys of dogs with experimental renal hypertension and of human beings with hypertension associated with nephrosclerosis should be confirmed

by the newer methods for extraction and testing of this substance. In early experiments, the difficulty was that renin, which seemed to present at least some of the basic requirements for the hypothetical pressor substance of experimental renal hypertension, lacked any vasoconstrictor effect when perfused in saline solution through the lower half of a toad or the leg or tail of a dog from which the blood had been washed out. Two groups of investigators (Braun-Mendez and collaborators and Page and collaborators) independently discovered that renin is not directly pressor and that although it is the key substance of the humoral mechanism its effect is due to the interaction with a substrate in the blood, with the resulting formation of an entirely new substance possessing vasoconstrictor and therefore pressor properties. To this latter substance the South American investigators gave the name hypertensin while Page and collaborators named it angiotonin. The term hypertensin is now generally accepted. As a result of these earlier observations, Landis, in 1940, wrote: "The evidence that renal ischemia raises the blood pressure by a humoral mechanism seems unassailable." However, even to this day, some observers have concluded that there is no peripheral vasoconstrictor substance in the blood of hypertensive animals.

Although there is general agreement that in the acute phase of experimental benign renal hypertension, in the malignant phase of experimental renal hypertension and in various forms of hypertension associated with renal insufficiency in man (such as eclampsia and acute glomerulonephritis), renin and hypertensin are demonstrable in the systemic blood, it has not been demonstrated that renin in appreciable quantity exists in the systemic blood of animals in the chronic benign phase of experimental renal hypertension or in human beings in the benign phase of essential hypertension.

Whether or not the normal kidney plays a part in the homeostatic regulation of normal blood pressure through the humoral mechanism of renal origin, which begins

with the excretion of renin, is still not established, but evidence is accumulating that it may play such a part. It has been shown, for example, that in shock the secretion of renin is induced and it is thought that the low blood pressure which produces renal ischemia is the cause. Although the existence of renin was discovered only about four years after the discovery of adrenalin by Oliver and Schafer and although the possible relationship of renin to the rise of arterial pressure in hypertension was obvious to the original investigators, nevertheless more than forty years passed before the existence of this substance was fully established. One of the reasons for this was the failure of some investigators to corroborate the original findings of Tigerstedt and Bergman. Many investigators who attacked this problem were really dealing with putrefactive pressor amines, not with renin, when they obtained pressor effects from the intravenous injection of autolyzed but not of fresh renal pressed juice.

Renewed interest in renin arose with discovery of the method of producing persistent hypertension in animals by constriction of the main renal arteries. The existence of a substance like that of Tigerstedt and Bergman in crude and even in more purified extracts of kidney was quickly confirmed. It was shown, moreover, that, as already indicated, the physiologic effects on the circulation resulting from the intravenous injection of this substance are not really due to the renin itself, which is not a vasoconstrictor, but are caused by hypertensin, the effective pressor substance formed by the interaction of renin upon a substrate (α_2 pseudoglobulin) in the blood plasma.

Page and Helmer noted that when renin is incubated with plasma or with serum, angiotonin (hypertensin) is formed, but that continued incubation results in the destruction of the angiotonin. This led them to believe that the continued action of the renin was responsible for the destruction of angiotonin. Muñoz and his collaborators, however, showed that this inactivating

effect of renin could be eliminated whereas the capacity of the renin to produce a pressor substance remained unaffected. This led them to postulate the existence of another enzyme associated with impure renin to which they gave the name hypertensinase. Page and collaborators later conceded the existence of such an enzyme and coined the name angiotonase for this enzyme to correspond with their nomenclature. This is a hydrolyzing enzyme or group of enzymes with the ability to destroy hypertensin *in vitro*. It is present in the blood plasma, serum, laked blood corpuscles and extracts of organs, especially intestine, kidney, pancreas, spleen and liver. Intestinal mucosa is the richest animal source of this enzyme. Blood serum and plasma that are not hemolyzed contain only a relatively small amount. An enzyme exactly like hypertensinase in its chemical and physiologic properties may be extracted from various plants, especially from wheat bran (Gollan, Richardson and Goldblatt). The chemical and physiologic properties of this enzyme have been described in detail in other publications.

Various names have been suggested for the different constituents of the humoral mechanism but the tendency at the present time is to accept the terminology originally suggested by the South Americans:

Renin (an enzyme from the kidney which enters the blood stream through the renal vein and interacts with hypertensinogen).

Hypertensin (a polypeptide formed by the action of renin. It is the active vasoconstrictor substance).

Hypertensinogen (a globulin in the blood plasma upon which renin acts to form hypertensin).

Hypertensinase (an enzyme in the blood and in extracts of some organs capable of inactivating hypertensin).

The chemical and physiologic properties of the various constituents of the humoral mechanism have now been described in great detail in several publications and will not be included at this time. The details about the method of assay for the various

constituents will also be omitted from this report.

Mechanism and Site of Formation of Renin. Little is known about the exact mechanism and site of formation or release of renin, despite the vast amount of work that has been done on the properties of the various constituents of the humoral mechanism in experimental hypertension. Even at the present time, there are those who, like Grollman, question the existence of preformed renin in the kidney and who consider that it is merely the product of autolysis *in vitro*. His experiments may merely indicate that in the renal tissue of the living animal there exists a renin precursor (prorenin) which is transformed into renin as it leaves the living cell and that the same transformation can also occur *in vitro*. Phenomena of this kind are known to occur in the case of other proteolytic enzymes of which trypsin is a good example.

Just what it is that occurs in the kidney with a constricted renal artery leading to the release or formation of renin sufficient to cause hypertension is not yet known. The observation of decreased oxygen consumption by the ischemic kidney or by ischemic renal tissue has been confirmed, but the significance of this phenomenon has been questioned on the ground that the reduction may have been due to the death of a certain number of cells and not to uniform interference with the function of living cells. The continuous inhalation of 100 per cent oxygen for forty-eight hours failed to lower the blood pressure of hypertensive dogs and the inhalation of 7 to 10 per cent CO₂ did not cause a greater rise of blood pressure in such dogs. This has been interpreted as unfavorable to the view of a hypothetical ischemic factor in the pathogenesis of experimental renal hypertension. Cruz Coke,³³ however, has concluded that tissue anoxia, especially renal, plays an important part in the humoral mechanism of renal hypertension. The demonstration that the cytochrome C concentration and the activities of cytochrome oxidase and succinic dehydro-

genase are greatly diminished in slices and homogenates of kidneys of hypertensive dogs may be subject to the same criticism as the experiments on oxygen consumption. The significance of these observations cannot be evaluated at the present time and more work should certainly be done in this field.

Most *in vitro* experiments on the origin of renin have indicated that it originates in the cortex of the kidney, and especially in the lining epithelium of the convoluted tubules. The finding that extracts of the aglomerular fish kidney contain no renin proved of no great significance because it was shown later that marine fish kidneys which do possess glomeruli also do not contain renin while the kidneys of fresh water fish do possess it in considerable amount. An explanation for this difference has not yet been found. Renin can be detected in the kidney of the dolphin which is a marine animal. The involuting tubular portion of the mesonephros of the pig embryo decreases while that of the developing tubular portion of the mesonephros increases, and renin cannot be extracted from kidneys in which the proximal tubules have been destroyed by sodium tartrate poisoning. These facts indicate that the convoluted tubules are the most probable site of origin (production and storage) of renin or at least of prorenin, if this exists. The exact nature of the stimulus which brings about the release of renin or prorenin has not yet been determined. The idea suggested by Page and his collaborators that reduction of intrarenal pulse pressure rather than decreased blood flow to the kidney is what determines the release of renin and the formation of vasoconstrictor substance depends entirely upon the demonstration of a pressor substance in the blood by perfusion of the rabbit's ear. This method is not accepted as a specific test for renin or angiotonin so it is questionable just what significance should be attached to these experiments. Even the assumption of a presumable change from intermittent to continuous pressure beyond the site of the afferent glomerular

arterioles is not justified for the very reason that a pulse pressure in the glomerulus has never been proven. Braun-McCord has stated unequivocally that "the idea that diminished pulse pressure within the kidney causes the liberation of renin has no solid experimental proof." The reduction of blood flow through the functioning components of the kidney (glomerular and peritubular capillaries) is another possible stimulus for the formation and release of these substances. That there is a reduction in the blood flow to the kidneys in most cases of essential hypertension affecting both kidneys equally, as well as in the early stages of renal hypertension, is an established fact but there is still some question as to whether permanent reduction of the blood flow is necessary for persistence of hypertension in animals. The answer to this question must await better and more direct methods than are available at present for repeated determinations of renal blood flow before and after constriction of the renal artery. Page and his collaborators have concluded that reduction of blood flow is not a necessary condition for the development of hypertension because, by indirect methods they have found that occasionally in animals no permanent reduction occurred in the blood flow to the kidney, despite a slightly increased blood pressure. For the demonstration of true renal ischemia, Chasis and Redish require that the ratio of renal plasma flow (diodrast clearance) to tubular excretory mass (maximum tubular secretion of diodrast) should be calculated since reduction of diodrast clearance alone does not necessarily mean renal ischemia. Smith and his co-workers consider that the available evidence favors the view that the renal ischemia so frequently observed in essential renal hypertension is a secondary event, and that the primary event is the circulation of a humoral substance of unknown origin which brings about efferent arteriolar spasm with progressive and parallel reduction in renal blood flow which they consider characteristic of essential hypertension. Others believe that the afferent arteriolar

spasm is due to hypertensin produced by renin in the blood, but in experimental renal hypertension this begins only after the renal artery is constricted; in man, therefore, it should begin only when the blood vessels (intrarenal arteries and arterioles) are stenotic.

Dock demonstrated the existence of a normally perfusable vascular bed in the kidneys of human beings with benign hypertension, especially when the perfusing fluid was kerosene, but this does not justify the conclusion that perfusion of blood through the kidney *in vivo* is normal in such individuals. Despite the obvious objection to the method, it is of interest that there was a great decrease in the rate of perfusion (even of kerosene) through the kidneys of patients with uremia due to arteriosclerosis, glomerulonephritis and pyelonephritis. Too little is known about the anatomy of the renal vascular bed and the effective circulation through the functioning components of the kidney to permit any conclusions from experiments of this kind about the effect of intrarenal stenosing vascular disease or of any other pathologic process capable of producing similar hemodynamic disturbances. The existence of intrarenal large arterial and arteriovenous anastomoses would nullify the value of most perfusion experiments. The recent studies of Trueta³⁴ indicate that such anastomoses do exist and that even on the basis of vasospasm, blood may be shunted away from the cortex in sufficient quantity to account for cortical ischemia.

The possible part played by the juxtaglomerular apparatus in the humoral mechanism of experimental renal and of human hypertension has not yet been determined with certainty. This anatomical structure, which is situated in the distal portion of the afferent arteriole of the glomerulus, has been described in detail by Goormaghtigh³⁵ and others. Goormaghtigh has reported an increase in the size of the juxtaglomerular apparatus and in the number and size of the afibrillar and sometimes granular or vacuolated cells of this

apparatus in the kidneys of rabbits and dogs with renal hypertension. He has also concluded that the afibrillar and granular cells may have a local or even a general secretory or humoral activity and may therefore have a direct relationship to the hypertensive principle. Afibrillar cells are common in the normal kidney of the rabbit, but Goormaghtigh has found an increase in the number of afibrillar and granular cells in the juxtaglomerular apparatus of rabbits made hypertensive by constriction of the main renal artery. He thinks that the afibrillar cells are connected with the arteriolar tone and that the granular cells are the source of the pressor substance. Dunihuc³⁶ and Kaufmann³⁷ have confirmed his findings and agree with his conclusions. Grace and Smith, however, have drawn attention to the great variation in the appearance of the arteriolar media and in the size and structure of the juxtaglomerular apparatus in normal man and animals and have cautioned that because of species differences (for example, the absence of granular cells in the kidney of man and dog), interpretation of the effects of ischemia must be contingent upon a more complete study of normal kidneys. The development of cytologic changes in the juxtaglomerular apparatus, interpreted by some investigators as indicative of endocrine activity, does not constitute convincing proof of the origin of an endocrine substance or precursor in this structure.

No direct convincing evidence has been offered to the present time that any special cells in the juxtaglomerular apparatus or preglomerular arterioles actually are the source of a chemical factor which constricts afferent or efferent glomerular or peripheral systemic arterioles. There is, therefore, no good reason as yet for accepting the view that this apparatus is the regulator of glomerular blood flow or the indirect cause of hypertension. The presence of renin in extracts of kidneys of developing pig embryos, in which a juxtaglomerular apparatus has not been identified, rather militates against this view. For the present it is best to

say that the functional significance of the juxtaglomerular apparatus in its relation to hypertension has not yet been determined with certainty.

The possible part played by the vasoexcitor material (VEM) and vasodepressor material (VDM) of Shorr and his collaborators³⁸ in the pathogenesis of experimental renal hypertension is yet to be determined. This subject will be discussed separately by Dr. Shorr in these seminars.

Shipley, Helmer and Kohlstaedt²⁹ have discovered a pressor principle in the blood of cats, dead as the result of certain undiagnosed natural causes, of D.D.T. poisoning, or of prolonged hypotension resulting from large withdrawal of blood. Intravenous injection of the plasma of such animals into cats bilaterally nephrectomized two days before caused a sustained elevation of blood pressure for as long as five hours but had no effect on normal cats. This effect occurred with or without anesthesia and even in the pithed, nephrectomized test animals. The new pressor principle appears to be distinct from renin, angiotonin, pepsitensin, hydroxytyramine or tyramine because of the difference in contour and duration of the pressor response and the difference in the conditions under which the response was observed. This principle was not found in the blood plasma of bilateral nephrectomized cats poisoned with D.D.T. in which prolonged hypotension had been produced by excessive bleeding or in animals made uremic by bilateral nephrectomy. It was not found in the blood plasma of normal living cats or of normal cats which had been killed suddenly by various means. They concluded that a moderately prolonged period of hypotension (with concomitant diminished blood flow and/or blood pressure within the kidneys) is necessary for the production of this pressor principle. They have not yet isolated this substance in pure form but have concluded that it appears to be a protein; it does not pass through a dialyzing membrane or ultrafilter and is heat-labile. The active substance is partly but not completely precipitated

at pH 4 by saturation of the extract with sodium chloride or by 0.6 saturation with ammonium sulfate. Although it has been demonstrated that renin does appear in the blood in the state of hypotension due to excessive bleeding, the amount of renin present is not sufficient to account for the pronounced and sustained pressor action of the hypertensin produced by the renin in the amount of plasma used in the experiment mentioned above. Injection of a fresh solution of renin extracted from kidney, capable of producing hypertensin *in vitro*, did not cause the same marked or sustained pressor response in the pithed, bilaterally nephrectomized cat. The fact that this new pressor substance produces such a sustained effect is of great interest. There does not appear to be any obvious connection between this pressor substance and the substances described by Shorr and his collaborators. The significance of this contribution to the problem of the humoral mechanism of hypertension and the regulation of normal blood pressure remains to be determined.

On the basis of experiments on renal hypertension in the rabbit, Pickering has concluded that only the initial phase of this type of hypertension is due to the renin-hypertensin mechanism and the persistence of the hypertension is not due to a neurogenic mechanism, as proposed by Ogden, but to another humoral mechanism. Because the pressor substance involved in the latter is not of renal origin, it is not identical with that of Shipley and his collaborators. More work is required before the exact nature of the mechanism involved in the acute and chronic phases of experimental renal hypertension can be considered established.

Antirenin. The entire subject of antirenin is a separate chapter which will not be discussed at great length here because it is not yet established that antirenin is specifically responsible for the antipressor effects originally described by Wakerlin and his collaborators.⁴⁰ These investigators found that in the serum of rabbits, dogs and guinea pigs (but not of the horse) injected subcu-

taneously or intramuscularly with renin from various species (not with homologous renin) a substance develops in the blood which is capable of neutralizing *in vitro* the acute pressor effect of an intravenous injection of renin. They regard this principle as analogous to an antibody, antienzyme or antihormone and suggested for it, the name antirenin. The injection of heat-inactivated homologous or heterologous renin does not induce the formation of antirenin in either normal or hypertensive dogs. After a normal or hypertensive animal has developed a high titer of antirenin large doses of homologous or heterologous renin may be injected intravenously without producing any change in the blood pressure. Wakerlin and his collaborators and we have found that repeated injection of heterologous renin subcutaneously or intramuscularly into hypertensive animals causes a fall of blood pressure to normal within a period of several months and that similar injections into normal animals for several months will prevent the development of renal hypertension when the renal arteries are constricted. Although he was the first to produce antirenin and was inclined at first to attribute these effects to antirenin, Wakerlin now considers that antirenin is not responsible for the prevention or cure of hypertension. We consider that the evidence on which he repudiates the significance of antirenin is not conclusive. This phase of the problem requires more investigation.

The possible application of the results obtained in animals to the treatment of human hypertension is beset with the difficulty that homologous renin does not induce the development of antirenin and the fact that human beings respond with a pressor effect to the intravenous injection of only homologous (human) renin.

SUMMARY OF THE SIMILARITIES AND DIFFERENCES BETWEEN ESSENTIAL HYPERTENSION IN MAN AND EXPERIMENTAL RENAL HYPERTENSION

Under this heading I can do no better than to repeat practically verbatim what I

have already written under the same title before.

In two recent books on the subject of experimental hypertension, divergent views were expressed about the mechanism of elevation of the blood pressure. Goldring and Chasis⁵ concluded that the weight of the evidence was against identity of the primary mechanism in human essential and experimental renal hypertension. They postulated the existence of a primary humoral mechanism of unknown origin to which a renal component may contribute a secondary and accessory effect. Braun-McNendcz and his collaborators,⁸ including Dexter who recently translated their book into English, have adopted the view that human essential hypertension in both the benign and malignant phases is primarily of renal origin. The existence of many similarities between any two processes or substances does not necessarily prove their identity, but I believe as they do that experimental renal hypertension faithfully reproduces human essential hypertension in most respects and that, for the present at least, it may be well to entertain the view that essential hypertension in man may be of renal origin.

In both types of hypertension there may be no significant disturbance of renal excretory function (the benign phase); or there may be pronounced renal excretory functional disturbance with uremia (the malignant phase), depending entirely, in experimental hypertension, upon the degree of constriction of the main renal artery. The malignant phase of human hypertension also may be directly dependent upon the severity and distribution of the sclerosis and stenosis of the intrarenal arteries and arterioles. Although an increase in the concentration of guanidine in the blood has been demonstrated in the malignant phase of hypertension in animals and man, this has little or no significance in relation to the cause of the hypertension because it occurs also in bilaterally nephrectomized animals that have azotemia but no elevation of blood pressure. In both types of hyper-

tion, cardiac action is increased but cardiac rate and output, volume, viscosity and peripheral flow of blood and venous pressure remain unaltered. In both man and animals, pulmonic arterial pressure also remains unaltered when the hypertension is uncomplicated by left ventricular failure as indicated by a normal right heart. In the benign phase of hypertension in both human beings and animals, cardiac hypertrophy chiefly involving the left ventricle develops. Medial hypertrophy of the aorta and arteries also occurs in both man and animals. In the malignant phase of both, essential hypertension in man and experimental renal hypertension in animals, many organs show the same typical vascular lesions (arteriolar necrosis, fibrinoid degeneration and necrotizing arteriolitis) which are recognized as characteristic of this condition.

The response to medical treatments of great variety is practically the same in both human and experimental renal hypertension. In both types of hypertension the blood pressure tends to go to higher levels with gain in body weight. The effect of a high protein diet is still undetermined. In both man and animals, hypertension associated with unilateral renal disease may be cured by excision of the diseased kidney, provided the other kidney is normal. Bilateral nephrectomy does not result in a rise of blood pressure in either man or animal, this despite the rapidly developing, profound azotemia. Sympathectomy, partial or extensive, may result in at least a temporary fall of blood pressure in human hypertensives without affecting the cause of the primary hypertension but there is little or no effect as a result of this procedure in animals. Whether or not this difference exists because the dog does not assume the erect position, with its consequent hemodynamic effects on the vasomotor apparatus, cannot be stated with certainty at the present time. The fact that after sympathectomy the blood pressure falls profoundly in some cases only when the patient is in the vertical position, that it rises again when

the horizontal position is assumed and that it returns to the original high level in a considerable number of hypertensive patients, favors the probability of a renal humoral mechanism in which the vasoconstrictor substance is presumed to act directly on the musculature of the peripheral arterioles and not by way of the vasomotor nerves. This is in keeping with the conclusions of Prinzmetal and Wilson¹⁴ and Pickering¹⁵ as a result of their studies on the pathogenesis of human hypertension.

The frequent fall of blood pressure which appears in the late stage of pregnancy in animals with experimental renal hypertension remains as unexplained as a similar fall which has been observed by obstetricians in some hypertensive, pregnant women. The observation of polydipsia and polyuria in rats with experimental renal hypertension has not been emphasized in human hypertension and has not been reported in hypertensive dogs although the diuretic effect of renin injected intravenously into dogs has been mentioned.

Renal blood flow is reduced in most cases of human hypertension and in experimental renal hypertension. The direct studies of blood flow through the human kidney do not demonstrate clearly the physiologic effect of sclerosis of the afferent arterioles because the presumable vasospasm of the efferent arterioles, which results in a high glomerular filtration fraction, tends to mask the sclerosis. Although the interference with afferent blood flow is definite in animals and obviously brought about by constriction of the main renal artery, the same indirect signs of efferent vasospasm and increase of glomerular filtration fraction have been reported in hypertensive animals. In both humans and animals, this effect may be secondary to the primary humoral mechanism of renal origin which results from the hemodynamic disturbance produced by the preglomerular vascular disease.

The existence of renin has been demonstrated in the renal venous blood of ischemic kidneys of both humans and animals and the intravenous injection of renin or hyper-

tension gives the same indirect evidence of different vasospasm. In acute hypertension, whether benign or malignant; renin has been demonstrated even in the systemic blood of dogs and in patients with hypertension due to acute glomerulonephritis or eclampsia. The failure to demonstrate it in the systemic blood in human and experimental renal hypertension in the chronic benign phase may be attributable to the amount of blood used for the tests being inadequate or to the lack of sensitivity of the method for its detection. Whether the humoral mechanism is effective in only the relatively acute stages of hypertension and whether, as has been suggested, there is in the later stages a greatly increased sensitivity to hypertensin; whether another humoral mechanism is involved or whether the later stage of the hypertension is on a neurogenic basis, remains to be determined. Comparison of the pharmacologic effects of renin and the circulatory dynamics in hypertensive animals shows a parallelism that is striking but this does not mean that the chemical mediation of hypertension by means of renin has been proved either for animal or man. The participation of other pressor substances, such as epinephrine, tyramine, pitressin and guanidine, can be excluded from serious consideration.

Although the elevated systolic pressure of hyperthyroidism in man is relieved by thyroidectomy, thyroidectomy has no effect on essential human or experimental renal hypertension. It is doubtful that any of the known endocrine organs play a primary part either in essential hypertension associated with vascular disease in man or in experimental hypertension in animals. There is no definite evidence for the view that the hypophysis plays a primary or secondary part in the pathogenesis of renal hypertension, but there are definite indications that the adrenal cortical hormones do play a secondary part in the development and maintenance of experimental renal hypertension and perhaps of human hypertension. In experimental renal hypertension, the adrenal cortex plays its part presumably

by influencing the production of hypertensinogen. This action is evidently exerted by an effect on the liver which is probably the source of this protein.

The many similarities between human essential hypertension associated with renal vascular disease and experimental renal hypertension suggest but do not prove that the former may also be of renal origin. Even if the renal origin of this form of hypertension should become established, it would still remain necessary to determine the cause of the arterial and arteriolar sclerosis which, when it affects the kidneys to a sufficient degree, initiates the humoral mechanism of the hypertension. The failure of animals to develop widespread arterial and arteriolar sclerosis, even after years of hypertension without accompanying impairment of renal excretory function (the benign phase), does not lend support to the view that hypertension is a sufficient condition for the production of vascular sclerosis. It must be admitted, however, that this may mean only that the blood vessels of animals are less sensitive than human vessels to the effect of increased intravascular tension alone although they appear to be even more sensitive to the conditions which determine the necrotizing vascular changes of the malignant phase of hypertension. Because the probable primary significance of renal arterial and arteriolar sclerosis has been indicated by experimental studies, the cause of vascular disease has now become the most important problem in the future investigation of the pathogenesis of hypertension.

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Participation of Hepatorenal Vasotropic Factors in Experimental Renal Hypertension*

EPHRAIM SHORR, M.D.

New York, New York

THE purpose of this paper is to supplement Dr. Goldblatt's review of experimental hypertension in this seminar with a consideration of the evidence obtained in this laboratory for the participation of recently described vasotropic principles of renal and hepatic origins in experimental renal hypertension.¹⁻³

Our studies grew out of the important contribution of Chambers, Zwiefach and their associates⁴ to the significance of the vascular reactions of anesthetized animals subjected to prolonged hemorrhagic hypotension or traumatic procedures. By direct visualization of the peripheral blood vessels in the mesentery and omentum of animals in whom hemorrhagic and traumatic shock was induced these investigators were able to recognize two consecutive stages in the shock syndrome which are characterized by opposite types of vascular behavior. The initial compensatory phase was apparently related to a reduction in blood volume, the subsequent decompensatory phase to the period of inadequate peripheral blood flow. The reaction of the peripheral vascular apparatus to blood loss *per se* was found to be essentially compensatory in nature—an attempt to reduce the capacity of the vascular tree without drastically curtailing the blood supply to vital tissues. This compensatory response is characterized by a hyper-reactive condition of the peripheral

blood vessels as evidenced by an increasingly enhanced reactivity of the terminal muscular vessels (the metarterioles and precapillaries) to epinephrine and an increase in their spontaneous vasomotor movements. This type of heightened reactivity persists even when the blood loss is sufficiently acute to precipitate collapse of the animal. Resultant capillary ischemia and restriction of peripheral blood flow to the most direct thoroughfare channels, the metarterioles, serve to maintain an active venous return of blood from the tissues until shortly before death. With prolongation of the profound hypotensive state, hyperreactivity was gradually superseded by a state of hyporeactivity, characterized by a progressive decrease in epinephrine reactivity and by slowing and finally complete cessation of spontaneous vasomotor caliber changes in the terminal arterioles and precapillaries. Loss of these restraining compensatory influences on peripheral circulation results in diversion of increasing amounts of blood into the capillary side channels from which it is inefficiently returned to the active circulation. This, in turn, leads to eventual failure of the venous return to the heart and to peripheral circulatory collapse. Once the hyporeactive stage has fully developed, transfusions are only of transient benefit, a state of irreversibility to replacement therapy having been reached. That blood-borne

* From the Department of Medicine, Cornell University Medical College and The New York Hospital, New York, N. Y. The work described in this paper was begun under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Cornell University Medical College, and continued under grants from the Josiah Macy, Jr. Foundation, the Eli Lilly Company and the Postley Hypertension Fund.

factors were responsible in large measure for both the compensatory vasoexcitor and the decompensatory vasodepressor effects was evident from the passive transference to anesthetized normal rats of effects corresponding to the reactions of the terminal blood vessels in the mesentery of the shocked animal at the time the blood sample was obtained.⁵

Vascular and humoral changes in the course of the development of experimental shock are summarized in Figure 1.

The significance of these observations lies in the demonstration of a constant participation in the shock syndrome of blood-borne vasotropic principles with specific actions on the terminal vascular bed, of such a character as to suggest that they are causally related to the initial compensatory vascular reactions to blood loss in the case of the vasoexcitor (VEM) and, in the case of the vasodepressor (VDM), to the progressive vascular deterioration which eventually results from prolongation of extreme hypotension.

This important contribution to the concept of shock provided the stimulus for laboratory studies which were designed to explore this concept further and, specifically, to investigate the sites of origin of these vasoexcitor and vasodepressor principles as well as the mechanisms leading to their formation and destruction.^{6,7} These studies have involved a combination of *in vivo* and *in vitro* procedures whose correlation was made possible by utilization of the rat meso-appendix technic of Zweifach and Chambers⁵ for the detection of vaso-excitor or vasodepressor activity in blood or tissue extracts. By means of this procedure in which the mesentery, specifically the meso-appendix, of the anesthetized rat is exteriorized for visualization it is possible to quantitate the extent of vasoexcitor and vasodepressor activity. This is done by determining the degree to which the response of the terminal vascular bed to the topical application of epinephrine is enhanced, as in the case of VEM, or depressed, as in the case of VDM; and further by

noting the duration of these alterations in epinephrine reactivity.

Sites of Origin of VEM and VDM. The initial group of experiments was designed to trace the tissue origins of these vasotropic principles and to determine whether they represented products common to all tissues exposed to the relative anoxia prevailing in shock or whether their formation was limited to specific tissues. Experimental hemorrhagic and traumatic shock was induced in dogs, rabbits and rats. At appropriate times during the compensatory and decompensatory phases of the shock syndrome a variety of tissues was removed and prepared for study as for microrespiration experiments. These tissues included the liver, cardiac, skeletal and smooth muscle, kidney and spleen. Saline extracts were prepared and assayed by the rat meso-appendix method.

Bio-assays of tissues removed during the compensatory, hyper-reactive stage of shock, at a time when significant amounts of VEM had appeared in the blood stream, showed that the genesis of VEM could be related only to the kidney cortex, the saline extract of which invariably contained considerable amounts of this factor. The saline renal extracts produced vascular effects in the test rat identical with those induced by the blood-borne VEM. Corroboratory evidence for the renal origin of VEM was provided by the absence of VEM in the blood stream in experimental hemorrhagic and traumatic shock induced after exclusion of the kidneys from the circulation.

Similar extracts of tissues of animals allowed to pass into the decompensatory, hyporeactive stage of shock, as determined by the presence of VDM in the blood, showed that the tissue origins of VDM were restricted to the liver, spleen and skeletal muscle. The liver was quantitatively the most significant source of this principle. The amount in skeletal muscle was smaller, particularly in hemorrhagic shock, its concentrations being proportional to the duration of the limb ischemia. In traumatic shock which followed the application of

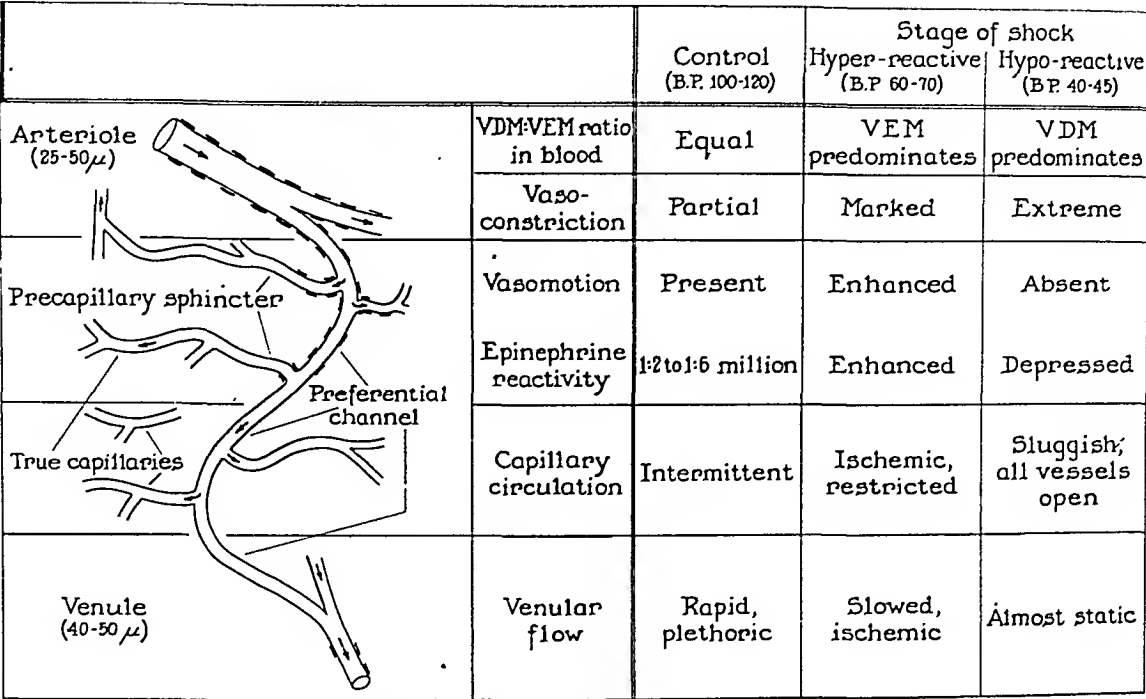


FIG. 1. Diagrammatic representation of the circulation in the terminal vascular bed of the omentum and mesentery in the normal state, and during the hyperreactive (VEM predominates) and hyporeactive (VDM predominates) stages of experimental shock. (Reprinted from SHORR, ZWEIFACH, FURCHGOTT and BAEZ. *Tr. A. Am. Phys.*, vol. 60, 1947.) (After Zweifach and Chambers.)

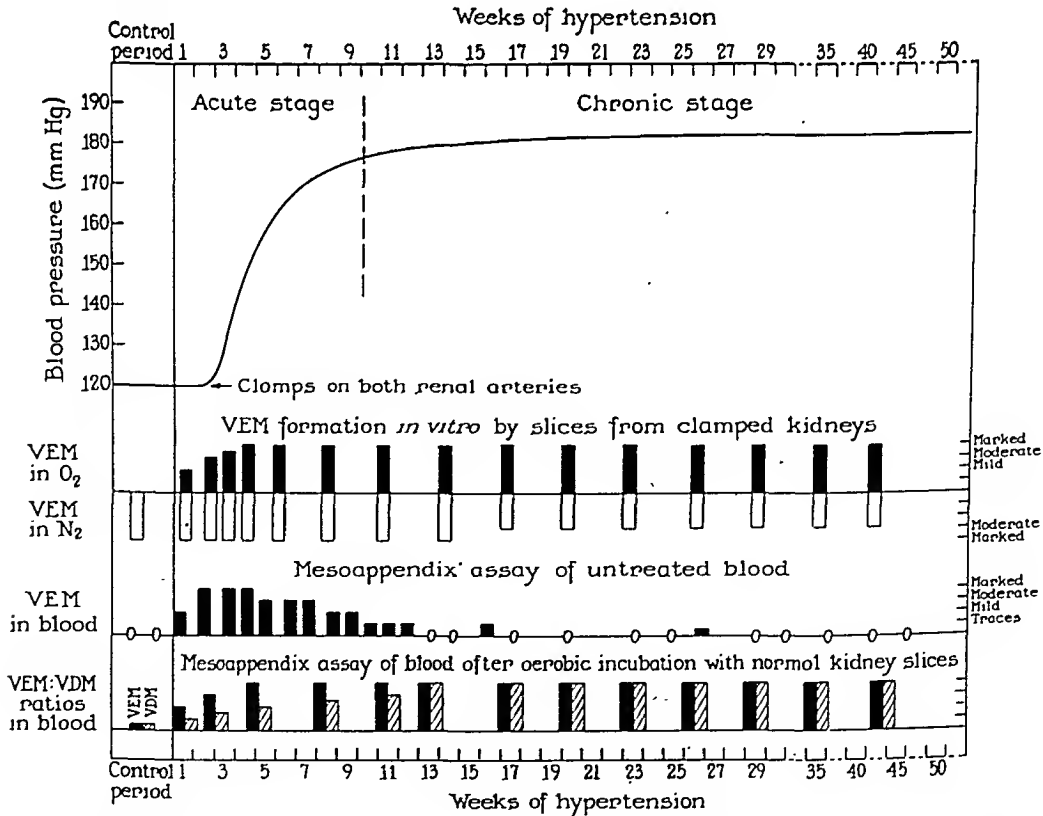


FIG. 2. Metabolic and humoral alterations in hepatorenal vasotropic factors in renal hypertension. (Reprinted from SHORR, ZWEIFACH, FURCHGOTT and BAEZ. *Tr. A. Am. Phys.*, vol. 60, 1947.)

tourniquets for six to ten hours, high concentrations of VDM were present in the saline washes of the muscles from the occluded limbs. It should be stressed that the formation of VDM by the liver was not related to hypotension *per se* but was uniformly confined to the decompensatory phase of the syndrome.

Mode of Origin of VEM and VDM. Having determined the tissues of origin, the next problem was to establish the mode of production of these vasotropic substances. In view of the difficulties presented in interpreting results in the living animal, *in vitro* procedures were employed by which specific environmental factors could be varied. Since tissue hypoxia prevails during shock, the influence of this environmental condition was first investigated. The same variety of tissues as well as brain cortex was obtained from normal animals and prepared as for microrespiration experiments. The tissues were then exposed to anaerobiosis *in vitro* for periods of two hours or longer in a Ringer phosphate or Krebs' bicarbonate medium. Control experiments were carried out under aerobic conditions. None of these tissues produced either VDM or VEM under aerobic conditions; under anaerobic conditions VDM was formed by the same tissues from which it was found to originate in the living animal, namely, liver, skeletal muscle and spleen. Only one tissue, renal cortex, was found to produce VEM anaerobically.

Inactivation of VEM and VDM. The third aspect of these studies was related to the persistence of VDM in the blood stream during irreversible shock despite transfusions, as contrasted with its rapid disappearance after injection into the normal test rat. It seemed probable that mechanisms existed in the healthy animal for the removal of this factor whereas the animal in irreversible shock had lost this property. This question was likewise studied by *in vitro* procedures. These consisted in the exposure of a variety of tissues from normal animals to VDM under aerobic conditions for a period of two hours. It was found that only

the liver possessed a mechanism for inactivating VDM oxidatively. This finding led to an investigation of the possibility that mechanisms might also exist for the aerobic inactivation of VEM. Such a mechanism was found to exist in the renal cortex and to a smaller extent in the liver.

It was also observed that the VDM inactivating mechanism in the liver was progressively damaged by prior exposure of the liver to anaerobic conditions. Upon restoration of oxidative conditions after two hours of anaerobic incubation a marked deterioration of the VDM inactivating capacity of the liver was regularly observed. A similar depression of the capacity to inactivate VDM was characteristic of the liver during the decompensatory, irreversible stage of shock, an observation which appears to provide an explanation for the persistence of VDM in the blood in irreversible shock despite the temporary restoration of oxidative conditions by transfusions. This is believed to comprise a crucial defect since the body can no longer liberate the vascular bed from the decompensatory action of VDM. During the compensatory phase, when the animal remains recoverable by transfusion, the VDM inactivation capacity of the liver was found to be unimpaired.

These observations have provided a basis for a concept of shock which can be briefly summarized as follows: The initial reaction to blood loss involves a reduction in renal blood flow sufficient to initiate anaerobic processes in the kidney which lead to the formation of VEM. This principle predominates in the blood stream and leads to the development of a type of vascular hyperactivity favorable to the maintenance of an adequate circulation in the face of reduced blood volume. During this phase of shock, in which the renal vasoexcitor dominates vascular behavior, the animal is recoverable by transfusion. If, however, the shock is prolonged and hypotension profound, the renal blood flow is virtually abolished and there is no further release of VEM into the blood stream. The reduction in blood flow to the liver is now sufficient

to initiate anaerobic processes in that organ. These lead to the formation of VDM and its release into the blood stream in amounts eventually sufficient to dominate the behavior of the terminal vascular bed. The vascular effects of VDM are decompensatory in character and make for progressive reduction in the effective blood volume with terminal peripheral failure. Once this stage is well established, transfusions are of temporary benefit since VDM will continue to dominate vascular behavior because of the damage sustained by the liver VDM inactivating system as a result of the previous hepatic anoxia. Considerations of space have permitted only a very brief and incomplete description of our experiments dealing with the participation of VEM and VDM in experimental and traumatic shock. For a more detailed account the reader is referred to other publications from this laboratory.^{6,7}

Before considering the participation of these vasotropic principles in experimental renal hypertension we may recapitulate the characteristics of these two oppositely acting principles and the systems which govern their formation. The formation of both VEM and VDM *in vitro* is limited in a normal kidney and liver to states of reduced oxygen tension. Under aerobic conditions VDM is inactivated by the normal liver, VEM by the normal kidney. These phenomena represent a type of Pasteur reaction analogous to the limitation of lactic acid formation by the normal tissue to anaerobiosis and to its disappearance by oxidation or storage under aerobic conditions. The VEM-forming and inactivating mechanisms are restricted to the renal cortex. It has not yet been possible to determine which type of liver cell is involved in VDM formation and inactivation. VDM and VEM exert diametrically opposite effects on the terminal vascular bed. VEM enhances the reactivity to epinephrine and increases vasomotion of the metarterioles and precapillaries; by augmenting the constrictor phase of the vasomotion of the precapillaries it serves to restrict the blood flow through the true capillary bed. VDM, on the other hand,

reduces the epinephrine reactivity of the metarterioles and precapillaries, depresses vasomotion and by prolonging the dilator phase of the precapillary sphincters, favors the filling of the capillary bed. These opposite vascular effects have led us to postulate that these vasotropic principles may represent components of opposite action in a homeostatic system participating in the regulation of peripheral blood flow. In the blood stream of the normal animal, these principles apparently exist in an equilibrium at low concentrations, blood from such animals giving a neutral reaction in the rat meso-appendix test. In the course of development and progression of the shock syndrome this equilibrium is shifted first in one and then in the other direction. During the initial compensatory phase there is a preponderance of VEM associated with vascular hyper-reactivity. During the subsequent decompensatory stage VDM preponderates with the resultant development of hyporeactivity. Preponderance of one or the other of these vasotropic principles is an expression of the reaction of the organism to a type of stress requiring profound vascular readjustments, namely, a reduction in effective blood volume, and is a reflection of the effects of reduced oxygen tensions on specific metabolic processes in the kidney and liver. Our findings as to the participation of VEM and VDM in the syndrome of experimental renal hypertension can now be projected against this background.

*Vasotropic Content of Blood during Acute and Chronic Renal Hypertension.*² Dogs were made hypertensive by the application of Goldblatt clamps to the renal arteries. Prior to the application of the Goldblatt clamp, 0.5 cc. of heparinized whole blood gave a neutral reaction when injected into the normal rat for bio-assay by the meso-appendix technic. Within thirty minutes of the partial constriction of the renal artery VEM appeared in the renal vein blood and a few hours thereafter could be detected in the peripheral blood. Blood from such dogs continued to show pronounced VEM activity during the period in which the blood pres-

sure was progressively rising. VEM disappeared from the blood when the blood pressure had become stabilized in the hypertensive range in dogs with two renal clamps, or with one kidney clamped and the other removed, or when the blood pressure had fallen to normal levels in dogs with one kidney clamped and the other intact. In the last group clamping of the second kidney resulted in the reappearance of VEM during the subsequent rise in blood pressure; on stabilization of the blood pressure at new hypertensive levels VEM again disappeared from the blood stream.

Evidently the partial constriction of the renal artery by the Goldblatt clamp rapidly led to the release of VEM by the clamped kidney and to its predominance in the blood stream throughout the stage of acute hypertension. Once the blood pressure had stabilized at the hypertensive level this preponderance disappeared, the blood again giving a neutral reaction. On the basis of our *in vitro* studies of the mechanism of VEM formation it seemed probable that the appearance of VEM in the blood stream was related to the temporary renal hypoxia resulting from the clamping of the renal artery. The return of a neutral reaction of the blood at chronic hypertensive levels might be attributed to restoration of a more adequate blood flow at these higher levels of blood pressure. Our next group of experiments were designed to test the validity of these hypotheses.

*VEM Mechanisms in the Clamped Kidney of the Hypertensive Dog.*³ It will be recalled that *in vitro* studies showed that VEM production by the healthy kidney took place only under anaerobic conditions, the kidney slice forming none in oxygen and actually inactivating VEM under aerobic conditions. Similar studies were now carried out on kidneys removed at intervals after the partial constriction of the renal artery by a Goldblatt clamp with the induction of hypertension. Within five and one-half hours and for as long as forty-five weeks after the partial occlusion of the renal artery, the kidney was found to have undergone

transformation into an organ which now elaborated VEM continuously even on aerobic incubation. This situation is comparable to the derangement of the glycolytic mechanism in cancer cells by which lactic acid is formed in both oxygen and nitrogen. Studies of clamped kidneys removed at all stages in the hypertensive syndrome showed a persistence of this metabolic defect even in those animals with only one kidney clamped and whose blood pressure had returned to normal. The clamped kidneys also exhibited a progressive impairment of their capacity to inactivate renal VEM on aerobic incubation *in vitro*. The basis for the aerobic production of VEM by clamped kidneys of hypertensive dogs would appear to reside in the loss of the renal mechanism for inactivation of VEM. As a consequence the homeostatic mechanism within the cell, by means of which VEM formation can be regulated, becomes deranged so that VEM is formed continuously under conditions which would ordinarily check its formation. Although the initial damage to the VEM inactivating system would appear to have its explanation in the reduced oxygen tension which follows the application of the clamped kidney, there appears to be no present explanation for the persistence of this defect during the stage of chronic hypertension when the blood pressure has risen to a level which is sufficient to maintain an adequate blood flow through the kidney as judged by the maintenance of its excretory function. Studies of the oxygen consumption of the kidney at intervals as long as forty-five weeks after the application of the clamps have shown the oxygen consumption to remain within the normal range, suggesting that the blood supply to the kidney has been adequate for its oxidative requirements.

We have also investigated the time relationship of the transformation of this "Pasteur reaction" by which a normally anaerobic process occurs under aerobic conditions. This was done by observing the effects of acute renal ischemia on the *in vivo* and *in vitro* formation of VEM.⁸ Occlusion of the renal circulation in rats for ten to

twenty minutes was followed by a transient hyper-reactivity* to epinephrine of the terminal blood vessels in the meso-appendix. With more prolonged renal ischemia (twenty to ninety minutes), persistent hyper-reactivity developed, the vessels becoming 20 to 200 times more responsive to epinephrine for at least sixty minutes, the period of observation. With renal ischemia lasting 150 to 240 minutes, a gradual deterioration of the VEM mechanism occurred, little or no vascular hyper-reactivity resulting.

The *in vivo* changes were shown to be related to specific alterations in the mechanisms for VEM formation and inactivation by means of *in vitro* incubation studies of ischemic kidneys. Kidney slices ischemic for ten to thirty minutes before incubation resembled a normal kidney, forming VEM only anaerobically. After forty to ninety minutes of ischemia, kidney slices produced VEM even under aerobic conditions. With more prolonged ischemia (120 minutes or longer), there was a progressive impairment in the ability of the kidney to form VEM both aerobically and anaerobically, as well as a deterioration of the renal mechanism for VEM inactivation. These experiments appear to be relevant to the findings with the clamped kidneys of hypertensive dogs and would suggest that the initial period of renal hypoxia following partial occlusion of the renal artery may be responsible for the alteration in the renal VEM mechanism whereby VEM is formed both aerobically and anaerobically. They provide no explanation, however, for the persistence of this metabolic defect in the clamped kidney during the period in which the blood flow has become adequate as a result of the hypertension.

*Vasotropic Content of "Neutral" Blood during the stage of Chronic Hypertension.*¹ The possibility was explored that the actual concentrations of VEM were high in the blood but that they were neutralized by equivalent amounts of VDM. Such a state might be anticipated if the renal and hepatic principles were counterparts of a homeostatic system. Exploration of this hypothesis was

accomplished by utilizing the ability of healthy kidney tissue to inactivate VEM *in vitro* under aerobic conditions without a comparable inactivation of VDM. The inactivation of VEM by aerobic incubation of blood with normal kidney slices would thereby unmask any VDM which was present and permit its detection. When this procedure was carried out with bloods of normal animals, no VDM could be detected by the rat meso-appendix test. When, however, "neutral" blood from dogs in chronic hypertension was similarly treated, large amounts of VDM were invariably revealed, suggesting that a new equilibrium had been established with higher concentrations of both factors. It is of interest that the new equilibrium level is generally achieved at about the time the blood pressure is being stabilized at a new hypertensive level.

Similar studies were carried out on the blood of twelve subjects with essential hypertension, using normal healthy adults as controls. The results were identical with the findings in normal dogs and those with chronic renal hypertension. Prior to aerobic incubation with normal kidney slices, bloods from normal controls were neutral; those from the hypertensive patients were either neutral or produced a slight vasoexcitator effect in the test rat. Following incubation, bloods from the normal subjects remained neutral whereas those from the chronic hypertensives induced a profound VDM effect in the test rat. These findings establish another point of similarity between experimental renal hypertension and essential hypertension in man.

*Relation of the Adrenals to Formation of VEM.*⁹ The necessity of intact adrenal cortical function for the maintenance of experimental hypertension and the hypotension which invariably follows adrenalectomy in normal animals, prompted an investigation of the state of the renal VEM mechanism following adrenalectomy. At various intervals after adrenalectomy in rats, rabbits and dogs the capacity of the kidney to form VEM under anaerobiosis was

studied *in vitro*. Three procedures were employed: (1) adrenalectomy; (2) adrenalectomy plus a high sodium chloride intake and (3) adrenalectomy plus sodium chloride and desoxycorticosterone (0.1 mg./Kg. daily). The renal capacity to form VEM under anaerobic conditions *in vitro* was found to become progressively impaired and in most instances was completely abolished even in animals maintained on high salt intakes. However, kidneys removed from adrenalectomized animals maintained on desoxycorticosterone acetate and salt for ten to fifteen days postoperatively, behaved like normal kidneys with respect to VEM formation. Observations were also made on the mesenteric blood vessels of adrenalectomized rats during the development of the syndrome. As adrenal insufficiency developed the vessels exhibited a progressive unresponsiveness to epinephrine as well as a progressive inability to respond to the intravenous administration of VEM. These experiments appear to establish the necessity of an intact adrenal cortical mechanism for the proper functioning of the renal VEM mechanism.

SUMMARY

We are now in a position to attempt a synthesis of the evidence for the participation of hepatorenal vasotropic factors in experimental renal hypertension. Shortly after the partial constriction of the renal artery by a Goldblatt clamp, significant amounts of VEM appear first in the renal vein blood and then in the peripheral circulation. The mechanism responsible for this shift in humoral equilibrium appears to be a specific alteration in renal metabolism as a result of which VEM is formed aerobically as well as anaerobically. This situation is indicative of a breakdown of the normal intracellular homeostatic mechanism by which *in vitro* VEM formation can be regulated by variations in oxygen tension. Acute *in vivo* and *in vitro* experiments suggest that this derangement is brought about by the period of hypoxia attendant upon the initial reduction

of renal blood flow which follows application of the clamp.

This defect in the renal VEM mechanism of the clamped kidney persists throughout the syndrome. Nevertheless, a preponderance of humoral VEM prevails only during the period of rising blood pressure. When the blood pressure has been stabilized at hypertensive levels, presumably with the restoration of an adequate renal blood flow, the blood again becomes "neutral." This neutrality is due to the appearance in the blood stream of increasing amounts of VDM which eventually reach a concentration adequate to neutralize the heightened concentration of VEM. The neutral state therefore represents the establishment of a new equilibrium between VEM and VDM at greatly augmented concentrations of both factors. A similar situation exists in the blood of patients with essential hypertension. The reasons for the persistence of the hypertensive state when the blood has again become neutral remains a matter for further study. The persistence of this defect in the renal VEM mechanism in dogs with one kidney clamped and the other intact and in whom the blood pressure has returned to normal, suggests that the unclamped hypertrophied kidney is inactivating the excess VEM which is continuously elaborated by the clamped kidney. A relation of the above phenomena to the adrenal cortex was brought out by experiments which showed that kidneys from adrenalectomized animals could no longer form VEM *in vitro*. Desoxycorticosterone, but not NaCl, restores this mechanism to the kidney of the adrenalectomized animal.

COMMENTS

At the present stage of this study we would prefer to limit a consideration of these observations to the descriptive level and to place emphasis on the regularity with which these vasotropic principles appear in the blood and the uniformity with which specific derangements develop in the renal VEM mechanisms during experimental renal hypertension. That a causal relationship exists

between these derangements and the development of renal hypertension cannot be definitely established on the basis of present data.

It should be pointed out that during the acute stage of renal hypertension the blood contains not only an excess of VEM but increased amounts of renin and hypertensin (angiotonin) as well. The question therefore arises whether or not VEM constitutes a distinct entity apart from renin and hypertensin. Some information has been obtained that this is the case.¹⁰ Its differentiation from renin, *per se*, is evident from its heat stability and the fact that it is dialyzable. Involvement of renin in VEM elaboration by the kidney cell remains uncertain. Thus, the unclamped hypertrophied kidney of the dog in which transient hypertension has been induced by clamping one renal artery, has been found to be devoid of renin.¹¹ Nevertheless, we have found that such kidneys form VEM under anaerobic conditions *in vitro*. The kidney of the adrenalectomized dog was noted by Goldblatt to have a normal renin content.¹² Such kidneys do not form VEM anaerobically even when incubated with normal plasma containing an abundance of renin substrate.⁹ It is conceivable, however, that the failure of VEM formation under these circumstances might be due to the absence of an appropriate intracellular substrate.

The differentiation of VEM from hypertensin is more difficult. Not only are both heat stable and dialyzable, but the kidney extracts containing renin, by means of which hypertensin is prepared *in vitro*, are almost invariably contaminated with VEM which is not destroyed during the preparation of hypertensin. We have, however, observed no correlation between the pressor activity, which is the essential action of hypertensin, and the VEM activity of such hypertensin preparations. This would suggest that whatever VEM activity is exhibited by these preparations is due to the initial contamination of the renin extracts with VEM. Experiments on isolated smooth muscle preparations have established the

musculotropic effect of hypertensin. Concentrated VEM preparations much stronger than those required to elicit epinephrine reactivity in the test rat are devoid of musculotropic effects.¹⁰ It has also been possible to dissociate VEM from hypertensin or hypertensin-like substances by occlusion of the renal circulation for long periods, e.g., four hours or longer, and its subsequent release.¹³ Although kidneys damaged by this procedure have lost the capacity to form VEM, they discharge material into the circulation with a distinct pressor effect attributed to hypertensin by Taquini.¹⁴ There are other differentiating features: In contradistinction to hypertensin, which is formed by the interaction of renin on an α_2 globulin in the blood, VEM is the product of intracellular metabolism. It is formed by renal cortical tissue, washed free of all blood and incubated in Ringer phosphate or Krebs' bicarbonate medium. Of particular significance is the circumstance that VEM appears to influence chiefly that part of the vascular bed distal to those arterioles on which hypertensin exerts its constrictor effect. Finally, the persistence of VEM in the blood stream during the chronic phase of hypertension contrasts with the disappearance of detectable amounts of renin and hypertensin in that stage of renal hypertension.

Several points concerning the action of VEM should be emphasized: First, the fact that this vasoexcitor principle is assayed by its potentiating effect on the constrictor response to epinephrine does not imply that the rôle of VEM in the organism consists in the potentiation of epinephrine. It is more likely that the vascular response to topically applied epinephrine represents a reaction more closely allied to the local reaction of the neuromuscular effector unit to a naturally occurring substance such as sympathin. Nor does the potentiation of the local response to topical epinephrine necessarily imply a corresponding change in the pressor response of the vascular system to intravenously administered epinephrine.

Second, the terminal vascular unit under consideration constitutes a unique segment

of the vascular tree which is under the dual influence of both systemic and local tissue factors; the metarterioles and precapillaries are the components most highly responsive to humoral substances. The primary functions of these vessels are concerned with the peripheral distribution of the blood and, through the process of vasomotion, with the adjustment of the pressure and volume of flow in the capillary bed relative to that in the feeding arterioles. Thus, the vasoexcitor principle, VEM, acts for the most part on a component of the vascular tree which is not directly concerned with the regulation of peripheral resistance and blood pressure. In this respect, VEM differs from the pressor agents, such as hypertensin, which act on the larger arterioles and which effect *acute* changes in blood pressure by their constrictor effects on these vessels. The potential effect of VEM on peripheral resistance and blood pressure would therefore have to be of an indirect and chronic character. What is suggested as a possible mechanism is the initial development, under the influence of VEM, of a sustained state of hyper-reactivity in the terminal metarterioles and precapillaries, a condition which we have observed to occur in the rat during the stage of acute hypertension.¹⁵ The persistence of such a state of hyper-reactivity would, in time, of necessity lead to the development of a tonically constricted state in the larger arterioles. This could come about either via a humoral mechanism or through a local axon type of reflex such as is normally responsible for arteriolar changes in response to changes in the capillary bed. Our studies are now being directed toward the exploration of these concepts.

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Conference on Therapy

Uses of Streptomycin

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. HARRY GOLD: The use of streptomycin is the topic of the conference today and the opening remarks will be made by Dr. Walsh McDermott.

DR. WALSH McDERMOTT: It was about three years ago that Dr. Waksman and his associates reported the discovery of the antibacterial agent, streptomycin. They not only discovered that the drug was effective *in vitro* against a number of gram-negative bacilli and the tubercle bacilli but also demonstrated that the drug was effective in certain experimental infections in animals. Within a year, Drs. Hinshaw and Feldman at the Mayo Clinic reported that streptomycin exerted a suppressive effect on the course of tuberculosis in guinea pigs and, soon thereafter, started their now well known studies of the effects of streptomycin in tuberculosis in humans.

The evaluation of the clinical effectiveness of streptomycin in infections other than tuberculosis has proceeded rapidly. In two successive issues of the *Journal of the American Medical Association* (132: 4, September 7th and 132: 70, September 14, 1946), the Committee on Chemotherapeutics headed by Dr. Keefer reported the results with streptomycin in 1,000 patients with various types of non-tuberculous infections. This report also contains information on the pharmacology and other fundamental aspects of the drug. Since this report is readily available, I shall endeavor to avoid duplicating its material.

Later we shall consider the use of streptomycin in tuberculosis separately. In other

clinical conditions, results with streptomycin have been most satisfactory in four types of infections: First, urinary tract infections caused by *Escherichia coli* or the other gram-negative bacteria which frequently produce infections of the urinary tract such as *Bacillus laetis aerogenes*, *Bacillus proteus*, Friedländer's bacillus and, in some instances, *Bacillus pyocyaneus*; second, meningitis caused by *Hemophilus influenzae*; third, tularemia and fourth, a miscellaneous group of infections, pneumonias, abscesses, peritonitis and the like caused by the same group of gram-negative bacteria which frequently produce urinary tract infections.

Equivocal results have been observed in acute brucellosis and in acute systemic infections due to food poisoning caused by the *Salmonella* group. The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans.

In the four types of infection in which streptomycin is of unquestioned effectiveness, the results have generally been as prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumococcus pneumonia. One of the greatest sources of difficulty in the use of streptomycin is the development by bacteria of resistance to streptomycin. This happens with more regularity and greater speed than in the case of other antibacterial agents. As a result, the total period during which the

drug may be used effectively is limited. In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed, the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance. However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and then by a relapse due to streptomycin-resistant organisms. The same general principle holds for all types of streptomycin-sensitive infections, including tuberculosis. Dr. Finland has made the interesting observation that, in urinary tract infection, the development of resistance to streptomycin by the gram-negative bacilli is appreciably reduced, if not eliminated, by maintaining the urine in a neutral or alkaline state.

Streptomycin should be used in the treatment of *Hemophilus influenzae* meningitis although an alternate type of effective therapy is available. In the treatment of *Hemophilus influenzae* meningitis, it must again be borne in mind that resistance may develop rapidly and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective. In Friedländer's pneumonia, there is a rapidly necrotizing infection caused by an organism which is susceptible to both streptomycin and the sulfonamides. There is theoretical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug. Thus, it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases.

It may prove worth while to give streptomycin a trial in instances of *Salmonella* infection in which bacteremia is present but whether an effect is to be anticipated cannot be said at this time.

We may summarize the situation with

regard to the non-tuberculous infections as follows: Streptomycin is a potent agent for the treatment of *Escherichia coli* infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram-negative bacteria. It should therefore be used in serious urinary tract infections due to *Escherichia coli*, in other types of urinary tract infections caused by *Bacillus lactis aerogenes*, *Bacillus proteus*, Friedländer's bacillus and *Bacillus pyocyaneus*. It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is frequently caused by streptomycin-sensitive organisms. It is effective, and should be used, in the treatment of *Hemophilus influenzae* infections. It is as yet of undetermined and probably questionable value in infections due to *Salmonella* and the *Bacillus typhosus*.

More than a year ago, Dr. Muschenheim, myself and our associates began our studies on the effects of streptomycin in human tuberculosis. This was prompted by the reports of Dr. Hinshaw and Dr. Feldman who noted that the administration of streptomycin produced a marked effect on the course of various types of tuberculous infections in man. Drs. Hinshaw and Feldman were very restrained in the conclusions which they drew from their observations but it was obvious from the data presented by them that their results with tuberculosis were unprecedented. Our own results have constituted a complete confirmation of their reports.

Up until now we have treated about forty-five patients with various types of tuberculosis. In general, three types of notable phenomena were observed in this group of patients: First, in the patients who were acutely ill, there was an abrupt or at least a rapid defervescence with accompanying symptomatic improvement. In some patients, the defervescence was as dramatic as the crisis of pneumococcus pneumonia. Second, in many of the patients there was a marked regression of the lesion. At times this regression continued to the

point of complete disappearance of the lesions demonstrable by x-ray. That specifically has occurred in patients with acute miliary tuberculosis. The third phenomenon was the development of bacterial resistance.

While the most dramatic results were observed in patients with acute hematogenous tuberculosis, it is not to be anticipated that generally favorable results will frequently be obtained in this condition. There are three reasons for this: The first is the high incidence of meningitis as a complication of acute miliary tuberculosis. Meningitis may be present either at the start of therapy or make its appearance during the second or third month. Secondly, relapsing miliary tuberculosis is to be anticipated and the third reason is one already indicated for other infections, namely, the development of resistance to streptomycin.

In meningitis without miliary tuberculosis, the situation is about the same as in the case of miliary tuberculosis. I would hazard the guess, on the basis of Dr. Hinshaw's experience, our own experience, the experience in the Veterans' Administration program and from the results in a few scattered patients treated here and there, that between one-fifth to one-tenth of patients with tuberculous meningitis will attain an eventually satisfactory result following the use of streptomycin.

Long-standing pulmonary tuberculosis, with cavitation and much fibrosis, has not, thus far, been appreciably benefitted by the administration of streptomycin. The surrounding infiltration may regress. The patient may feel better during this phase of the therapy. However, in every patient thus far, streptomycin-resistant strains of organisms have developed.

The form of tuberculosis in which the most satisfactory results have been observed has been the exudative disease of short duration with moderately advanced or even far advanced lesions. Here presumably there are no anatomic barriers to rapid arrest of the lesion. In this stage of the disease, effective antimicrobial therapy for

six or eight weeks may well spell the difference between success or failure. From the studies we have made on the resistance of the tubercle bacilli to streptomycin it seems that in the majority of patients resistance appears between the fourth and eighth week of therapy. Therefore, effective therapy with streptomycin is limited to a great extent to those types of tuberculosis in which it is possible to obtain a significant reversal of the course of the disease within a period of four to eight weeks. Exudative disease, with or without thin-walled cavities, is the type of pulmonary tuberculosis in which it is conceivable that this could happen and from our experience thus far it seems that it does happen.

Just one more point on tuberculosis. I think we have clear cut preliminary evidence that the development of streptomycin-resistance by the tubercle bacillus, demonstrable *in vitro*, is paralleled by clinical evidence of this resistance *in vivo*. Of the first eleven patients who developed bacterial resistance demonstrated *in vitro*, eight developed clinical relapses during therapy and in five of the eight, the relapses progressed to a fatal termination despite the fact that streptomycin therapy was continued. In each instance, the relapses occurred after a period of dramatic improvement. Therefore, I believe there can be no question but that the development of streptomycin resistance, demonstrable by *in vitro* tests, means that the usefulness of the drug in that particular infection has come to an end. I should like to point out that the development of drug resistance by organisms in the central nervous system may, however, proceed at an entirely different rate from that in those patients with infections of the lung.

Unlike penicillin, streptomycin has important toxic properties. Four types of toxic reaction have been observed: The first is the so-called histamine reaction, which does not occur with the presently available material and, therefore, no longer gives any concern.

The second type consists of various manifestations of delayed anaphylaxis or sensitivity reactions. These reactions are identical with drug fevers and rashes which are observed after the use of any number of drugs. When one encounters such a reaction, it is advisable to re-evaluate the need for therapy. Fortunately, in many cases of non-tuberculous infections, by the time the reaction appears the need for drug therapy is over and one can discontinue the use of streptomycin without endangering the patient. In tuberculosis, on the other hand, that is not the case and in such instances one must decide whether the tuberculosis or the sensitivity reaction carries the greater threat to the patient. Eosinophilia is another type of sensitivity reaction due to streptomycin. The eosinophilia is usually marked and may represent as much as 35 to 40 per cent of the white cell count. In one instance in our series, it was accompanied by tenosynovitis. No evidence of peripheral vascular disease has been noted thus far although eosinophilia of that degree has caused us some apprehension.

The third type of reaction, that of renal irritation, is evidenced largely by granular casts. This may be prevented by maintaining urine on an alkaline basis. It is difficult to establish whether normal kidneys are permanently damaged by this process. I think the evidence is highly suggestive, however, that kidneys previously damaged by other disease can be further damaged by streptomycin. Beyond doubt, renal insufficiency appears and progresses under the administration of streptomycin. This has now been noted by many observers. It is well, therefore, to be extremely cautious in the administration of streptomycin to any patient with known renal disease.

The fourth type of reaction constitutes the only serious drawback to the use of the drug from the standpoint of toxicity. It is a central nervous system reaction characterized by vestibular dysfunction and occasionally accompanied by deafness. Evidence of this type of reaction appears in all patients who receive 2 or more Gm. of

streptomycin daily for longer than three or four weeks. The reaction usually starts as a mild headache which gathers intensity within twenty-four hours and then disappears. The vestibular disorder then appears. It is not a true vertigo as a rotary component is lacking. There is however a very definite sensation of overshooting the mark; for example, in initiating a movement in any direction, the patients have the sensation that the movement is continuing after it has actually stopped. As a result, they may believe they are falling to one side or the other, or forward and may be acutely uncomfortable. There is considerable variation in the intensity of this reaction. In some patients, perhaps one-third, it is negligible and the symptoms can be elicited only on careful questioning. In another third, the symptoms are moderately acute for a period of a week or ten days and then subside almost, but not quite, completely. In the remaining third, or in perhaps a somewhat smaller number, the symptoms are much more severe and last longer. These patients are unable to sit erect in bed or move about with their eyes open but after these symptoms subside minimal vestibular dysfunction may persist for as long as sixty days and in some, they appear to persist indefinitely. Recovery from this vestibular dysfunction seems to occur by virtue of compensatory mechanisms and not by restoration of labyrinthine function. In some patients, this type of compensation may never occur or may occur only after many months of dysfunction. Dr. Hinshaw has observed, and it was also noted here and by others, that elderly patients do not effect compensation after the development of the reaction as readily as younger patients. This is a point of great importance to the urologist who is faced with the problem of urinary tract infections in men in their seventies.

Deafness, fortunately, is a rare symptom. In the Mayo Clinic and in the New York Hospital-Cornell series, it has been seen only under three conditions; in those patients who received very large doses of streptomycin, 5 to 10 Gm. daily, in those who

received the drug intrathecally and in patients with renal insufficiency. I should state that 3 Gm. a day, or at most 4 Gm., is the upper limit of safe dosage. Even this may prove toxic in patients with renal damage because of accumulation of the drug. The patients with deafness after intrathecal administration had meningitis and it is difficult to be certain whether the deafness was due to the disease or to the drug but, at least in some instances, it was probably due to the drug. It is safe to say that in patients with normal renal function in whom the drug is given intrathecally, deafness will rarely occur with a daily dose of 3 Gm.

DR. GOLD: The subject is now open for discussion. Are there any questions?

INTERN: In a recent issue of the Journal of Venereal Disease Information, there was a report of the use of streptomycin in specific and non-specific urethritis. I believe Dr. Kotcen has used streptomycin in gonorrhea caused by organisms resistant to a sulfonamide and penicillin. I wonder if we could hear from him and Dr. McDermott on its use in such cases.

DR. GOLD: How about it, Dr. Kotcen?

DR. HERBERT KOTCEN: Dr. Gold, I had the opportunity of using streptomycin in two patients who had penicillin- and sulfonamide-resistant gonococcus infections of the urethra. In one, a woman, there were thirty-two positive cultures during a course of treatment with sulfadiazine and/or penicillin. Thirty-six hours after streptomycin was used, the cultures became negative and remained so. The other patient was a young man who took sulfadiazine on and off for nine months and had five courses of penicillin. His cultures also became negative after 3 Gm. of streptomycin. Two other patients were treated with streptomycin. Both had an *Aerogenes* infection; in one, it was complicated by *Streptococcus alpha* and in the other, by a *staphylococcus*. Both had failed to respond to sulfadiazine and penicillin but responded to combined penicillin-streptomycin therapy. All of these patients received a dose of 2 Gm. of streptomycin daily for five days.

DR. GOLD: Dr. McDermott, did you have a comment?

DR. McDERMOTT: In summarizing the material so briefly, I omitted mention of certain types of infections by gram-positive organisms against which streptomycin is effective. One very important instance is bacterial endocarditis caused by organisms with a relatively high penicillin-resistance, such as those of the *Zymogenes faecalis* group and another is *staphylococcus* endocarditis caused by penicillin-resistant strains.

VISITOR: I would like to ask Dr. McDermott if he has had any experience with streptomycin in typhoid carriers and whether he ever used it orally in an attempt to sterilize the stools with respect to the typhoid organism?

DR. McDERMOTT: We have no experience along those lines. We have treated only six patients with typhoid fever. They were all early cases and were excellent for clinical evaluation since all had bacteremia at the time treatment was started. In four, there was no effect. Two patients did very nicely in terms of the progress of their typhoid fever but we do not know whether the favorable course was related to the streptomycin. It would be my guess that streptomycin would have only a temporary effect on the earlier state and that this would not persist after the streptomycin was discontinued.

DR. McKEEN CATTELL: I would like to ask Dr. McDermott whether we may not anticipate that, if streptomycin is widely used in the treatment of tuberculosis, most infections will eventually be of resistant strains?

DR. McDERMOTT: Dr. Cattell, I think we can almost guarantee it, if enough tuberculosis is treated with streptomycin. We do not know, of course, how long the strains remain streptomycin-resistant after the drug is discontinued. Thus far, the few which we have treated have remained resistant for as long as ninety days following a four-month period of therapy. However, it may be that in six months or so they revert to their original state of streptomycin-sensitivity.

I believe, and I am sure Dr. Muschenheim agrees with me, that the importance of streptomycin in tuberculosis lies not so much in its own potential for the cure of tuberculosis, as in the demonstration, by means of this drug, that it is possible to affect the course of the tuberculous infection with a chemotherapeutic agent. We hope that eventually there will be a better agent than streptomycin for the long pull in this disease.

DR. GOLD: Dr. McDermott, is there a record of a single patient with tuberculosis who has been cured by streptomycin?

DR. McDERMOTT: Oh, yes, I would say that of Dr. Hinshaw's patients with meningitis. Would you go along with that, Dr. Muschenheim?

DR. CARL MUSCHENHEIM: Those patients have been followed for six months or more but whether they could be called "cured," I think, is somewhat doubtful. I do not think that there has been any more evidence that tuberculosis is "cured" by streptomycin than that it is "cured" by any other method of treatment. I am talking about tuberculosis in general. I think that we still must speak in terms of "arrest" and that we still must expect relapses on the same basis and caused by the same influences as we have found in the past with other forms of treatment.

DR. McDERMOTT: The term "cure" should not be used. The action of streptomycin was originally described by Hinshaw and Feldman as "suppressive." Actually, all antimicrobial agents are "suppressive." Streptomycin is in no way different in its effect on tuberculosis than any other antimicrobial agent on other infections. What we should anticipate from streptomycin and future antituberculous agents is not a dissolution of all tubercle bacilli within the body, but rather the conversion of all, or nearly all cases, of certain types of active tuberculosis into the equivalent of the best results previously obtained by natural mechanisms.

DR. MUSCHENHEIM: I would like to refer to the statement made by Dr. McDermott that streptomycin is not the ideal drug in

the treatment of tuberculosis because of the development of resistance. I do not think that he intended to convey the impression that streptomycin could not be useful in a general program of treatment of all kinds of tuberculosis. He indicated that there are particular phases of tuberculosis, namely, the exudative ones in which the effect of streptomycin is most dramatic.

Another point concerns the fact that the effectiveness in tuberculosis may be of brief duration. Therefore, in applying streptomycin in association with other forms of treatment, such as surgery or collapse therapy of various kinds, we should choose the time very carefully. We do not want to shoot our bolt, so to speak, before we really need it.

DR. WALTER MODELL: This is the first time, I think, that I have heard Dr. McDermott advise the combined use of two chemotherapeutic agents. I wonder, in view of that, what he thinks about using streptomycin together with one of the sulphones, such as promin, which had been recommended some time ago as an effective antitubercular agent.

DR. McDERMOTT: Implied in your query is the view that the combined use of antimicrobial agents may materially diminish the development of resistance to either agent. There is impressive *in vitro* evidence that it may be so. This has been a subject of a great deal of debate and speculation.

The combined use of streptomycin and promin is now being tried out. It should take a relatively short period of time to find out whether promin is useful when combined with streptomycin because the development of resistance to streptomycin is so uniform.

DR. MORRIS PEARLMUTTER: How should one treat a fulminating case of influenzal meningitis, Dr. McDermott?

DR. McDERMOTT: I am probably not the one best qualified to answer that since I am not a pediatrician but I will answer it anyway. I would use streptomycin alone for a twenty-four-hour period. At the end of that time, I would be guided principally by the findings in the spinal fluid, especially by the

number of bacteria. They are relatively easy to demonstrate by the quellung test. If it fell from 1,000 to the order of about 20, I would continue the streptomycin but if the effects were not as impressive, I would most certainly switch to Dr. Alexander's immune serum and sulfadiazine. In the few patients whom we have treated, the results have been dramatic with streptomycin alone.

DR. PEARLMUTTER: Suppose the count dropped but slightly, would you then be inclined to treat the patient with all three agents?

DR. McDERMOTT: I would certainly see no objection to treating with all three or with a combination of two. Sulfadiazine presents no problems. Immune serum is rather expensive and so is streptomycin. I see no theoretical objection, however, to using all three agents together.

DR. GOLD: Dr. Levine, could we have an expression of opinion from you?

DR. SAMUEL Z. LEVINE: In a particularly fulminating case of influenzal meningitis, on the basis of Dr. Alexander's experience, it would seem wise not to postpone the use of the three agents in combination if the response to streptomycin alone were not dramatic. As Dr. McDermott pointed out, it cannot do any harm, except for the cost, and it may do a lot of good.

DR. McDERMOTT: I did not see Dr. Levine there or I would not have been so presumptuous as to answer that question.

DR. GOLD: Tell us something about the cost.

DR. McDERMOTT: As a matter of fact, in influenzal meningitis, the expense of streptomycin is not so great because one is usually dealing with an infant or small child. One-half Gm. to 1 Gm., depending upon the size of the child, is usually enough for a daily dose. The market price fluctuates but streptomycin is purchasable at this time for approximately \$4.00 for 1 Gm.

VISITOR: What has been the experience with the so-called minimal lesions in tuberculosis?

DR. MUSCHENHEIM: We have not treated minimal lesions although we had one case

which was virtually minimal. It was moderately advanced because there was a very tiny cavity. This promptly closed with streptomycin. The patient was a young colored girl who, with a good deal of bed rest, had failed to obtain an arrest of the disease. It was only because the disease has such a serious prognosis in her particular age, sex and race that we even considered treating her with streptomycin.

* In general, I believe, and I think Dr. McDermott agrees with me, that minimal cases should not be treated with streptomycin. We know nothing yet about the late toxic sequelae of the drug. Dr. McDermott has called attention to the eosinophilia which causes some concern since it might indicate serious, late sequelae. We hesitate to give streptomycin in these minimal cases because we are afraid of causing serious toxic effects in the treatment of a disease which has an almost uniformly favorable prognosis when treated by methods known to be safe.

VISITOR: If the organism becomes streptomycin-resistant, is the infection any more dangerous?

DR. McDERMOTT: That is a problem which has concerned us and about which there is no information. It certainly should be investigated. We must find out whether the continued administration of streptomycin after development of streptomycin-resistance produces a more fulminating type of infection.

DR. GOLD: How do you view the mechanism of the very rapid development of resistance to streptomycin in view of the more or less generally accepted idea that the development of resistance is due to the breeding out of resistant strains? Why does that happen so quickly in the case of streptomycin and relatively slowly in the case of penicillin? It is fundamentally the same type of process, breeding out the tolerant or resistant members of a strain.

DR. McDERMOTT: I think that the development of bacterial resistance proceeds by several mechanisms; breeding out is only one; mutation is another. There is evidence

that adaptive enzymes can be developed by bacteria. The selective breeding of chance developing mutants is generally believed to be the most reasonable explanation for most instances of the recognized resistances. Most organisms against which penicillin is effective show remarkable uniformity in their sensitivity *in vitro* among the individual members of a species. There are some exceptions such as the staphylococcus. It seems to be otherwise for streptomycin. The *Escherichia coli* against which streptomycin is so effective, for example, shows rather wide differences in the susceptibility of members of a species. A fundamental difference in the point of attack on the vital functions of the bacterial cells in the case of the two drugs may be one factor in explaining the ease with which streptomycin produces bacterial resistance. This applies to the mechanism of breeding out resistant members as well as to any other mechanisms by which resistance within bacterial cells may be developed.

INTERN: I would like to ask if the kidney damage caused by streptomycin is permanent or reversible?

DR. McDERMOTT: Some of it is certainly reversible. We had one patient, about thirty years old, who, in the course of a very serious tuberculous pneumonia, developed evidence of fairly marked renal damage during a sixty-day period of streptomycin therapy. The urea clearance fell to about 40 per cent of normal. During the second sixty-day period of treatment the renal damage subsided concurrently with the improvement in the tuberculous pneumonia. Another patient, who had only one kidney, suffered renal damage during the first course of treatment with streptomycin. A second course of treatment for ninety days, however, produced no further apparent damage, the blood urea nitrogen remaining somewhat above 30 mg. and the urea clearance below 20 per cent of normal.

DR. CATTELL: I would like to ask Dr. McDermott if he has tested the resistance of the organisms in the tuberculous patients before using streptomycin?

DR. McDERMOTT: We have in every case

and all of them were sensitive. This was also the case with the organisms which were tested by Dr. Youmans in Dr. Hinshaw's studies. I must emphasize that the conditions of the test are not such as to give one a wide sampling of the individual cells in a particular culture. No one has as yet carried out the necessary test of streaking out the culture and testing a number of different cells for sensitivity.

DR. GOLD: Do not all routine *in vitro* tests for sensitivity suffer from the same defect, namely, that they fail to separate out resistant from sensitive members in the sample which is being tested?

DR. McDERMOTT: That is so, Dr. Gold when the test is performed in liquid media. It is not so when the organisms are plated out. That is what is being done in the case of the staphylococcus, for example.

INTERN: I would like to ask if streptomycin has an effect on the hematopoietic system? I remember one patient in whom the platelet count dropped from 350,000 to around 40,000 after streptomycin administration. When the streptomycin was discontinued, the platelet count returned to normal.

DR. McDERMOTT: Was there any bleeding?

SAME INTERN: Yes, there was bleeding when the count was at the low point. The bleeding was the reason for the count. This patient had had typhoid fever and the gall-bladder was removed because he was a typhoid carrier. He then developed a typhoid abscess in the operative wound for which the streptomycin was given.

DR. McDERMOTT: Was he receiving a sulfonamide?

SAME INTERN: No.

DR. McDERMOTT: Such a reaction might be expected after a sulfonamide but I have never encountered it after streptomycin. There is a report of a patient with acute brucellosis treated with streptomycin who developed thrombocytopenic purpura from which he recovered completely. We have seen leukopenia and in one case it was associated with granulocytopenia. We have seen these reactions in patients with acute military tuberculosis in whom the possibility

of bone marrow involvement was also present.

DR. MUSCHENHEIM: Dr. Bunn told me of a patient with military tuberculosis who developed granulocytopenia which improved after the discontinuation of streptomycin. This seemed to rule out bone marrow infection due to tuberculosis.

DR. GOLD: Dr. McDermott, will you say something about the dosage and the preparations?

DR. McDERMOTT: By great good fortune, the original unit of streptomycin coincided with 1.0 microgram of the active substance. This makes it convenient, therefore, to express dosage in terms of weight of the drug.

DR. GOLD: Are doses expressed in terms of the pure crystalline substance?

DR. McDERMOTT: Yes, in terms of the pure streptomycin base. The material which is marketed is in the form of the hydrochloride or the sulfate and it is not pure. The label on the vial indicates the amount of the pure base to which the contents of the vial is equivalent. Thus, in a vial labeled as equivalent in activity to 1 Gm. of streptomycin base, the actual weight of the material in the vial may be greater than 1 Gm. because of the impurities. Because of the differences in the amount of impurities in different preparations, two vials labeled 1 Gm. streptomycin may contain different amounts of material while both represent the activity of the same amounts of pure streptomycin.

The material is soluble in water. It can be administered dissolved in distilled water. It is usually given by intramuscular injection.

For most infections, 1 to 3 Gm. daily is adequate. In tuberculosis, Dr. Hinshaw's group first used 1 Gm. and then 1.5 Gm. We used 3 Gm. from the beginning. There is no evidence that our patients have done any better than Dr. Hinshaw's. There is no evidence that large initial doses prevent the development of bacterial resistance; at least bacterial resistance has not been prevented by even such large doses of streptomycin as cause toxic effects. For most

urinary tract infections, I think 1 Gm. per day should be sufficient. In *Hemophilus* influenzal meningitis, the dose depends on the size of the child. I think 0.1 Gm. is the upper limit of safe dosage in an adult when the drug is administered by the intrathecal route. Larger doses than that are sometimes tolerated but are sometimes associated with toxicity. We would therefore advise using single doses of streptomycin no larger than 0.1 Gm. when given by the intrathecal route.

DR. GOLD: Do you prefer the interrupted intramuscular method of administration?

DR. McDERMOTT: Usually I do. In a non-fulminating infection, I would say that therapy during eighteen of the twenty-four hours would be adequate. In a fulminating infection, such as *Hemophilus* influenzal meningitis, injections should be given at three-hour intervals around the clock.

DR. GOLD: Not by intravenous injection?

DR. McDERMOTT: It is unnecessary.

DR. JANET TRAVELL: Does the material cause pain?

DR. McDERMOTT: Yes, the commercially available material of the past two years was painful to a variable degree. Highly purified crystalline material, at least 95 per cent pure, such as we used in the tuberculosis study, is no more painful than the best penicillin preparations.

DR. GOLD: Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

DR. McDERMOTT: No, but I believe that the large manufacturers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used.

DR. TRAVELL: Will that increase the cost?

DR. McDERMOTT: It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization. I doubt that it will materially increase the cost to the public in a competitive market if there is enough demand for it.

DR. PEARLMUTTER: Has streptomycin been given a trial in virus pneumonia?

DR. McDERMOTT: I do not know of any instances in which it has but I assume that it has. I would certainly be opposed to using it in atypical pneumonia. Although the drug is relatively non-toxic in comparison to some drugs, it is not innocuous and not to be used for self-limited, benign infections.

DR. GOLD: How does the problem of oral administration stand at the moment? Animal experiments show that it is absorbed by the oral route and that the fatal dose, by mouth, in mice, is just about three times that by subcutaneous injection. I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like five to ten times the parenteral dose, we might obtain perfectly satisfactory effects by the oral route. Have you any opinion about that?

DR. McDERMOTT: We have not pursued the subject because of the scarcity of the material.

VISITOR: At Bellevue Hospital a series of typhoid carriers was examined. First, the drug was given intravenously. There was no conspicuous effect on the typhoid organism. There was a high incidence of renal toxicity among these patients. Some of them were given the drug orally. There was apparently less renal irritation. For a time the stool cultures were negative but subsequently reverted to positive. I am not certain of the range of dosage when it was given orally; I think it was of the order of twice the intravenous dose.

ANOTHER VISITOR: Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

DR. McDERMOTT: Unfortunately, that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin.

INTERN: At a recent therapy conference on urinary tract infections we were left with the impression that the sulfa drugs are far more useful in these infections than strep-

tomycin. I wonder if you share those sentiments?

DR. McDERMOTT: In uncomplicated infections of *Escherichia coli*, which is the most common infection of the urinary tract seen by the internist and the obstetrician, I believe that sulfadiazine should be used first. While streptomycin is very effective against the *Escherichia coli* urinary infections, its greatest value in infections of the urinary tract does not apply to the *Escherichia coli* infections but to the infections by other organisms in the urinary tract and in those complicated by bacteremia or metastatic abscesses arising in association with obstructions of the urinary tract.

DR. GOLD: Dr. McDermott, as matters stand at the present time, would you be inclined to give streptomycin a trial in any infection which was found not to respond to penicillin or a sulfa drug, irrespective of whether the organism involved was a coccus or bacillus, gram-positive or gram-negative? To be sure, experience with streptomycin in some infections such as typhoid fever, bacillary dysentery and undulant fever has been disappointing and, in those few instances, one might be justified in withholding the drug but how about the large variety of other infections? Is the scope of streptomycin uses sufficiently defined to justify its omission in an infection in which penicillin and the sulfa drugs were considered and tried but proved ineffectual and in which it now seems that the patient is likely to die unless the infection is controlled?

DR. McDERMOTT: Yes, I think that streptomycin should be tried since there is evidence that some one of these agents will affect most bacterial infections. The virus infections are exceptions. I do believe, however, that reasonable indications should be present before streptomycin is used because of its fairly high toxicity.

DR. GOLD: Might you possibly first make an *in vitro* test for the susceptibility of the organism?

DR. McDERMOTT: Yes, that would help.

DR. GOLD: I am afraid our time is up.

SUMMARY

DR. MODELL: The conference this afternoon was on the subject of the uses of streptomycin. The experiences with the sulfa drugs and penicillin have been put to good use in speeding up the steps necessary for the proper clinical evaluation of this new antimicrobial agent and now, only about three years after the first clinical reports on streptomycin, a formidable volume of information has accumulated concerning its actions and uses. The material is now available in a highly purified form. Since, however, it still contains some impurities, varying in amounts in different preparations, a biologic assay is applied to the different lots. It is less confusing to express dosage in units of weight rather than in biologic units and, therefore, the labels on the vials describe the contents in terms of Gm. of pure streptomycin base. Streptomycin is freely soluble in water. It is suitable for all the common routes of administration. Not enough is known about its absorption by oral administration and it does not seem to be useful for systemic action by the oral route. It is most commonly given by intramuscular injection in divided doses. A dose of 2 to 3 Gm. daily appears to be adequate for the majority of infections in which it is useful. Larger doses are likely to cause too high an incidence of toxic effects.

Streptomycin is effective against most of the organisms which are inhibited by penicillin. In addition, however, it exerts a potent action against gram-negative organisms which are uninfluenced by penicillin. While bacteriologic experiments suggest a very wide field of usefulness for streptomycin, direct experience in the treatment of human diseases has greatly restricted the scope of its application. Experience thus far indicates that penicillin is preferable in those infections in which either of the drugs might be used because penicillin is non-toxic while streptomycin possesses toxic actions which are sometimes quite serious. There is also the fact that penicillin is administered in quantities measured in milligrams and streptomycin in quantities of grams and

these large amounts of the drug are not practical for some of the special techniques of administration such as suspension in wax and oil for delayed absorption. Thus far, streptomycin has been found especially useful in urinary infections caused by the *Escherichia coli* and some other gram-negative bacterial infections of the urinary tract such as the *Bacillus lactis aerogenes*, *Bacillus proteus* and *Bacillus pyocyaneus*. It is highly effective in Friedländer's pneumonia, *Hemophilus influenzae* meningitis and tularemia. It has also been found effective in pneumonias, abscesses, peritonitis and other infections caused by the gram-negative bacteria frequently found in the urinary tract. It appears to be without value in virus infections. One of the most stirring aspects of streptomycin action is the observation that it cures certain forms of animal tuberculosis and the now well established clinical experience showing that it may check some forms of human tuberculosis, especially those in the exudative stage. There was considerable discussion in the conference concerning the details of its rôle in the therapy of human tuberculosis.

Two other phases of streptomycin therapy received special consideration. There is some indication that different members of the same bacterial species show wide differences in susceptibility to streptomycin and it is now well established that for most infections, resistance to streptomycin is acquired quite rapidly, in a matter of days to weeks. This limits the application of the drug to brief courses of treatment and necessitates the use of fully effective doses from the outset. The next point is the matter of toxicity. Streptomycin is not an innocuous drug. In addition to the various allergic drug reactions such as skin rash and fever, it may produce serious renal damage, it may affect the blood-forming organs and it exerts an action on the central nervous system involving the vestibular apparatus and the eighth nerve causing vertigo, tinnitus and impaired hearing, some of the effects becoming permanent. These effects are apt to occur after prolonged use of the drug,

after three or four weeks. They are more frequent with the larger doses, doses larger than those usually necessary. One needs to keep them in mind, however, for the full scope of the applications of streptomycin has not yet been established and a good deal of exploration is still necessary to establish the full potentialities of streptomycin in

human infections. In the present state of our knowledge, there is justification in giving streptomycin a trial in serious bacterial infections in which the other specific antimicrobial agents have failed. It is suggested that an *in vitro* test of the sensitivity of the organism may help to establish the indication for its trial in such cases.

Clinico-pathologic Conference

Rheumatic Heart Disease, Bacterial Endocarditis and Cardiac Failure^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. B., (B. H. No. 118183), a twenty-two year old white, married draftsman, entered the Barnes Hospital for the first time on September 22, 1944, complaining of weakness. The family history was non-contributory. The past history revealed that the patient, in addition to the usual childhood diseases, had had scarlet fever at the age of six years and, subsequently, his mother had been told that the patient's heart had been damaged. At the age of nine, he was said to have had "rheumatism" for several days but he could recall no specific symptoms. From that time on he had been a thin, nervous individual who lacked physical endurance but he had had no further significant illnesses. His habits were good.

Six months before entry, the patient was given digitalis by his family physician although he could give no history of any cardiac symptoms at that time. He took the medication for one month and then discontinued it because of nausea. About seven weeks before entry, he developed increasing fatigability, so much so that he often fell asleep while working and at night slept twelve hours; his appetite also decreased. About five weeks before admission, the patient had a tooth extracted and a few days thereafter he noted the onset of fever which at one time was said to have been as high as 104°F. A non-productive cough, associated with generalized aching pains

in the chest and left arm, began and the patient again consulted his family physician who made a tentative diagnosis of tuberculosis; a chest film was negative, however, and the diagnosis was changed to chronic bronchitis.

One month prior to entry, small, painful red spots appeared on the tips of the patient's fingers and toes and a week later he began to note palpitation and dyspnea on exertion. Two weeks later, his ankles swelled and he was admitted to a rural hospital where he was given a sulfonamide drug four times daily for four days. He became very nauseated and totally anorexic and was transferred to the Barnes Hospital.

At the time of entry, his temperature was 37°C., pulse 92, respirations 24 and blood pressure 94/50. The patient was a well developed but poorly nourished, young, white male who lay quietly in bed and appeared chronically ill. The skin was pallid. Petechiae were noted on the skin of the back, hands and feet and there were small, tender, red lesions on some of the finger tips. The joints appeared normal. The conjunctivae were clear. The pupils reacted well to light and accommodation and fundoscopic examination was negative. The teeth were carious and the gums exhibited signs of infection. Examination of the lungs revealed them to be clear to percussion and auscultation. On inspection, the heart appeared hyperactive; a heaving

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

impulse occupied most of the precordium and a systolic thrill was easily palpable. On percussion, left border dullness enlargement extended 14 cm. in the fifth interspace and 13 cm. in the sixth interspace and right border enlargement was 3.5 cm. in the fourth interspace. The first sound was obscured by a very rough, harsh, blowing systolic murmur which could be heard all over the precordium as well as posteriorly. A mid-diastolic, low pitched, rumbling murmur was audible at the apex. The rhythm was regular. The spleen was palpable 4 cm. below the left costal margin and was slightly tender. The remainder of the abdominal examination was negative; there was no clubbing and the neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 4,320,000; hemoglobin, 12.5 Gm.; white cells, 9,500; differential count; juvenile forms, 2 per cent; stab forms 27 per cent; segmented forms, 60 per cent; lymphocytes, 11 per cent. Urinalysis; albumin, trace; sediment, occasional hyaline cast and occasional red blood cell. Stool examination: negative. Blood Kahn test: positive. Blood chemistry: non-protein nitrogen, 18 mg. per cent; total protein, 6.1 Gm. per cent; albumin, 3.5 Gm. per cent; globulin, 2.6 Gm. per cent. Blood sulfadiazine level (on entry): 10.5 mg. per cent. Venous pressure: 125 mm. of saline. Circulation time (decholin): 16 seconds. Vital capacity: 2700 cu. cm. Roentgenogram of the chest: "The cardiac silhouette is enlarged to the left and somewhat to the right. It has a globular appearance with prominence in the region of the pulmonary artery. The aorta is inconspicuous. There is tenting and irregularity of both leaves of the diaphragm, presumably as a result of adhesions from old pleurisy." Electrocardiogram: slurring and notching in lead I; T waves low upright.

Five consecutive blood cultures taken shortly after the patient entered the hospital were positive for alpha-hemolytic streptococci. A swinging temperature curve persisted and showers of new emboli were

observed. As soon as the blood culture results were known, penicillin was instituted in a dosage of 40,000 units every two hours intramuscularly. There was a prompt response to therapy as indicated by a fall in temperature and a great decrease in the number of emboli. The urine became entirely negative and subsequent blood cultures were all sterile. The blood Kahn test was repeated and on titration revealed 40 Kahn units. The patient denied any lesions suggestive of primary or secondary syphilis and no further antisyphilitic therapy was instituted during the hospital stay.

The patient continued to receive penicillin for nineteen days after which it was discontinued; he received a total of 5,850,000 units. He left the hospital on November 5th, 1944, to be followed in the Clinic.

Following discharge, the patient did progressively well. He had no further fever nor petechiae and three months after discharge was well enough to resume his work as a draftsman. Five months before his second admission, he had a number of teeth extracted at weekly intervals, each time with sulfadiazine prophylaxis. He was followed in the Clinic where his general condition continued to be good except that he failed to gain weight despite an excellent appetite. He was advised to re-enter the hospital in order to ascertain the cause for his failure to gain weight.

He was admitted on July 9, 1945, at which time the temperature was 37.2°C., pulse 100, respirations 24 and blood pressure 128/65. He appeared quite well. No petechiae were observed. The only changes in physical examination from those recorded on the previous admission were as follows: a definite early high-pitched diastolic blow was heard over the aortic area and along the left sternal border. The pulses were fuller than before and the pulse pressure had increased. The liver edge was felt 1 to 2 cm. below the costal margin. It was thought by one observer that the fingers were slightly clubbed.

Laboratory studies revealed the blood count, urinalysis and stool examination to

be entirely within normal limits. The blood Kahn test was negative. The vital capacity was 4400 cu. cm. and the corrected sedimentation rate 0.1 mm. per minute. The electrocardiogram showed only a full P-R interval. Because of the previously positive serologic test for syphilis, a lumbar puncture was performed and the findings were entirely negative. During his hospital stay the patient's course was entirely uneventful and he was discharged on July 14, 1945, to be followed in the Clinic.

He did quite well for a number of months, working as a radio repair man. One month before his third hospital admission, he developed an upper respiratory infection which was followed by a non-productive cough; at no time did he have fever. He recovered from the respiratory infection but subsequently had increasing dyspnea on exertion which soon became so severe as to incapacitate him. He also had episodes of paroxysmal nocturnal dyspnea and complained of frequent palpitation. Progressive edema of the ankles likewise appeared and the patient gained approximately 6 pounds. One week before entry, he noted pain in the upper abdomen and a feeling of fullness after meals. He had no other digestive symptoms nor had he had pain in the chest, night sweats or fever. He was readmitted to the hospital on March 5, 1946.

At the time of entry, his temperature was 37°C., respirations 24, pulse 90 and blood pressure 110/70. He appeared rather ill and in moderate respiratory distress. Orthopnea was particularly notable. There was a frequent, dry, hacking cough. The neck veins were markedly distended. There was some diminution of breath sounds over the right posterior chest but definite signs of fluid were not made out. A heaving precordial pulsation extended to the left mid-axillary line and the heart rate was 128 at the apex. The rhythm was irregular. The same harsh, systolic murmur previously noted was present and P₂ was accentuated. In the aortic area, the sounds were muffled and a diastolic murmur could not be made out. The liver extended 5 cm. below the

costal margin and was smooth and tender. The spleen was questionably palpable. There was 1+ ankle edema.

The laboratory findings were as follows: the red count, hemoglobin, white count and differential count were normal. Urinalysis: specific gravity, 1.022; albumin, 1+; sediment, negative. Stool examination: negative. Blood Kahn test: negative. Venous pressure: 240 mm. of saline. Circulation time (decholin): 44 seconds. Blood chemistry: non-protein nitrogen, 25 mg. per cent; total protein, 4.6 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 1.5 Gm. per cent. Blood cultures: no growth. Electrocardiogram: low voltage in lead I; auricular fibrillation, right axis deviation.

The patient was digitalized with digitoxin; his venous pressure soon fell to 140 mm. of saline and the circulation time to 30 seconds. Dyspnea, orthopnea, ankle edema and cough all disappeared and on a salt-free diet the patient became quite comfortable. He left the hospital on March 17, 1946, with instructions to maintain a salt-free diet and to take 0.2 mg. of digitoxin daily. Once during his hospital stay, one observer again described an early diastolic murmur at the aortic area and along the left sternal border. At no time were any of the peripheral manifestations of bacterial endocarditis noted.

Following discharge, the patient was essentially symptom-free except for mild dyspnea on exertion. One month before his fourth admission, he had the onset of two-pillow orthopnea and his ankles again began to swell. He had no fever, chest pain or any digestive disturbances. He re-entered the Barnes Hospital on July 1, 1946.

The findings on physical examination included a temperature of 37.2°C., pulse 84, respirations 18 and blood pressure 124/80. Physical examination was essentially unchanged from that recorded on the third admission except the neck vein distention was not so marked. Auricular fibrillation was again described and the liver, which was palpable 4 cm. below the right costal margin, was tender. The spleen could not be felt. No clubbing or edema was described.

The routine blood studies were all normal. The urine was negative except for a small amount of albumin. Blood cultures were all sterile. The venous pressure was 220 mm. of saline and the circulation time with decholin was 55 seconds. Films of the chest revealed no new findings. An electrocardiogram showed auricular fibrillation, right axis deviation, ventricular premature contractions and questionable digitalis effect.

The patient was seen in consultation by the dental surgeon and extraction of two badly diseased teeth was advised. Penicillin was given prophylactically and the teeth removed under local anesthesia. Subsequent to extraction, repeated blood cultures continued to be sterile and at the time of discharge on July 12, 1946, the patient was essentially symptom-free. He was again instructed to maintain a salt-free diet and to continue digitoxin. During his stay he had had no fever.

In the eight weeks following discharge, the patient had a gradual but progressive increase in dyspnea, ankle edema and non-productive cough and on September 6, 1946, he was re-admitted for evaluation of his cardiac status.

The findings on physical examination were not significantly changed from those noted previously. The laboratory findings of interest were a white count was 19,650; the differential count showed 2 per cent basophiles, 4 per cent eosinophiles, 12 per cent stab forms, 49 per cent segmented forms, 23 per cent lymphocytes and 10 per cent monocytes. Urinalysis revealed rare granular casts in the sediment. The venous pressure was 210 mm. of saline and the circulation time with decholin was 50 seconds. The total proteins were 4.7 Gm. per cent with 3.3 Gm. per cent of albumin and 1.1 Gm. per cent of globulin.

The patient remained in the hospital eight days; rest in bed combined with a salt-free diet and digitoxin were sufficient to restore cardiac compensation. He left the hospital on September 14, 1946, to continue the same therapeutic regimen.

He did fairly well and was able to return

to his work as a radio repair man. He was followed in the Clinic where he was given mercupurin intravenously at frequent intervals; prior to each administration of mercupurin, he took ammonium chloride. Digitoxin therapy was likewise continued but, despite these measures, the patient's ankle edema recurred and he developed increasing dyspnea both on exertion and at rest. Likewise, paroxysmal nocturnal dyspnea reappeared and his cough became worse. He remained at home in bed for several weeks during which period flatulence and belching likewise occurred; he complained of severe nausea but did not vomit. He entered the Barnes Hospital for the last time on December 12, 1946.

At that time, he appeared poorly nourished, depressed and extremely ill. Orthopnea was marked but there was no cyanosis. The significant physical findings included marked venous distention and a massive right hydrothorax. The heart was greatly enlarged and the precordial impulse was so severe as to shake the patient's entire chest with each beat. Rapid auricular fibrillation was present with a marked pulse deficit and a harsh, grade iv, blowing, systolic murmur could be heard all over the thorax. A mid-diastolic rumble was likewise audible at the apex. At the base, the grade iv systolic murmur could be heard but no aortic diastolic murmur could be made out. The liver extended 8 cm. below the costal margin. The spleen and kidneys were not palpable. There was 3+ pitting edema of the ankles extending up to the knees.

Laboratory findings were as follows: the complete blood count, urinalysis and stool examination were all within normal limits. Blood Kahn test: negative. Venous pressure: 300 mm. of saline; circulation time (decholin): 75 seconds. Blood chemistry: non-protein nitrogen: 22 mg. per cent; CO₂ combining power, 51.8 vol. per cent; chlorides, 92 mEq./liter. Blood culture: negative. Roentgenogram of the chest: "There is extensive enlargement of the cardiac shadow. The aortic knob cannot be seen. There is a prominence of the cardiac

shadow in the region of the pulmonary conus and left auricle. Compared with previous films there has been some increase in heart size. The lungs show evidence of congestion but otherwise are normal except for the diaphragmatic adhesions previously present." Electrocardiogram: auricular fibrillation, digitalis effect and right axis deviation.

The patient was placed on a regimen which included complete bed rest, a salt-free diet, digitoxin 0.1 mg. twice daily, ammonium chloride 1.0 Gm. three times daily and mercurhydrin 2.0 cc. every other day. Despite these measures, he failed to improve; indeed, his dyspnea and orthopnea increased and he was placed in an oxygen tent. Because of persistent nausea and vomiting, he was unable to take adequate food or fluids by mouth and had to be fed parenterally. The non-protein nitrogen gradually rose and before the patient's death reached a level of 111 mg. per cent. During his entire hospital course the patient remained afebrile. The sedimentation rate was within normal limits. His white count likewise was never elevated. In an attempt to achieve some degree of cardiac compensation, digitoxin was given intravenously in doses totalling 0.3 mg. daily but it was not effective; the marked pulse deficit persisted and the patient continued to do poorly. The possibility of acute rheumatic fever as an explanation of the patient's poor response to digitalis was raised and salicylate therapy was instituted but it likewise was without favorable results. The patient became obtunded and subsisted on subcutaneous 5 per cent glucose in water. The apical cardiac rate and pulse deficit increased further; breathing became slow, irregular and gasping and the patient lapsed into a coma. Death occurred on December 21, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient had a long history which illustrates many of the essential features of rheumatic endocarditis. The onset of the process apparently

occurred when he was six years old and when he was twenty-two he developed subacute bacterial endocarditis due to the alpha-hemolytic streptococcus. The latter complication was apparently cured by penicillin but subsequently recurrent cardiac failure appeared and finally led to death. Let us consider first of all the onset of the rheumatic disease. According to the history, this man had scarlet fever when he was six years old and very shortly thereafter his mother was told that his heart had been affected. This sequence of events raises the question of the relation of scarlet fever to rheumatic fever. Dr. Harford, would you open the discussion of this point?

DR. CARL G. HARFORD: Scarlet fever is considered to be one of the streptococcal infections which may precipitate an attack of acute rheumatic fever.

DR. ALEXANDER: Is that opinion well accepted or is there some debate about it?

DR. HARFORD: There are probably some differences in the views of various interested and informed persons but certainly the majority favor this concept which was set forth by Dr. Homer Swift, among others.

DR. ALEXANDER: Dr. Massie, would you care to comment?

DR. EDWARD MASSIE: I think the sequence described in this case is not an unusual one. Of course, scarlet fever *per se* need not occur, since a patient may have a streptococcal infection of the throat without a rash and develop rheumatic fever in much the same way. In other words, the manifestations of the original streptococcal infection may differ in various individuals whereas its relation to rheumatic fever is the same in all of them.

DR. ALEXANDER: We may, therefore, assume that the historic events outlined are not unusual and that this patient developed rheumatic fever as a consequence of scarlet fever when he was six. He did well from that time until he was twenty-two years old. He apparently received digitalis six months before his first admission here but we are unable to state why since he denied any cardiac symptoms at the time.

Seven weeks before his first entry, however, he noted the onset of fatigue and anorexia. Two weeks later, a tooth was extracted and one week after that and three weeks after the onset of fatigue, he had emboli and many of the signs and symptoms of bacterial endocarditis. Do the signs and symptoms of that disease usually develop over such a short period of time, Dr. Harford?

DR. HARFORD: I think it is a little difficult to be sure how long the patient actually had the disease.

DR. ALEXANDER: According to the history, three weeks elapsed from the onset of fatigue, which was his first complaint, to the time he noted emboli. What is your feeling on this subject, Dr. Massie?

DR. MASSIE: I saw this man in consultation at another hospital and was quite impressed by the rapidity of the development of the disease; indeed, I believed that it was one of the most rapidly developing cases I had ever seen. When I saw him, the diagnosis of bacterial endocarditis seemed quite clearcut and because at that time we were one of the clinics studying the effect of penicillin treatment on bacterial endocarditis, the patient was transferred to the Barnes Hospital. I might say that when I questioned the patient I had the impression that his symptoms prior to dental extraction were not particularly severe and I believed that the bacterial endocarditis was secondary to the extraction. In that case, the manifestations of the disease developed within a week.

DR. ALEXANDER: Are you impressed with the fact that he had no anemia when he was admitted, Dr. Moore?

DR. CARL V. MOORE: Anemia is certainly a characteristic finding in subacute bacterial endocarditis but there are cases such as this one in which anemia is not present.

DR. ALEXANDER: It was my feeling that anemia had not yet developed because of the very short duration of the entire process. After the diagnosis was confirmed by a number of positive blood cultures, the patient received 40,000 units of penicillin

every two hours intramuscularly for nineteen days, a total dosage of almost 6,000,000 units. Dr. Harford, what is the suggested period of treatment for this disease?

DR. HARFORD: In general, we believe that treatment should be continued for a longer period of time than was used in this case. We have seen relapses occur after two or three weeks of therapy and now believe that a period of six weeks is advisable. This man was treated at a time when penicillin was scarce and, therefore, the duration of treatment was shorter than would be used today.

DR. ALEXANDER: Would you comment on the dosage?

DR. HARFORD: The dose, of course, must be adjusted to that level which controls the disease. We usually begin with a dose of 50,000 units given every two hours intramuscularly. If sensitivity tests are done, a dose is usually advised which achieves blood levels four or five times the *in vitro* sensitivity of the organism. The clinician must base his judgment as to the efficacy of a given dosage on the temperature response, the results of repeated blood cultures and the patient's general clinical condition. If the original dose fails to control the process, the dosage should be doubled or even quadrupled.

DR. ALEXANDER: How frequently is drug-fastness observed?

DR. HARFORD: We observed two cases out of twenty-one in which the streptococcus recovered was definitely resistant to penicillin.

DR. C. V. MOORE: It is interesting, in considering the dosage that this patient received, to note that Dr. Loewe in some instances had given as high as 10,000,000 units per day in the treatment of penicillin-resistant organisms but even doses of that magnitude did not control all the cases in which the causative streptococcus was highly penicillin-resistant.

DR. MASSIE: Dr. Alexander, do you think that the very short duration of the patient's illness prior to treatment favors the good

results obtained with the relatively small dose over a short period of time?

DR. ALEXANDER: That thought occurred to me and I am going to ask Dr. Robert Moore to comment on that point when he shows us the microscopic sections. As you know, Dr. Moore has studied the healing process of this disease very carefully in patients treated with penicillin.*

This man's heart was extremely large. He had a loud, systolic murmur which could be heard all over the precordium and a low pitched diastolic rumble which was heard at the apex. From these signs, Dr. Massie, would you be able to predict the sites of the valvular lesions in the heart?

DR. MASSIE: Certainly the signs point to both mitral stenosis and mitral insufficiency. In addition, on several occasions an early basal diastolic murmur was heard and therefore one would consider the possibility that the aortic valve may have been insufficient.

DR. ALEXANDER: In view of the huge heart size, would you expect to find evidence of pericarditis?

DR. MASSIE: There may well be areas where the pericardial space is obliterated by fibrous adhesions but I doubt that physiologic constriction of the heart occurred. True constrictive pericarditis is rare in rheumatic heart disease.

DR. ALEXANDER: I was thinking more of pericardiomediastinal adhesions.

DR. MASSIE: I am sure that they will be found.

DR. ALEXANDER: Subsequent to his recovery from subacute bacterial endocarditis, the patient developed heart failure. Dr. Smith, I wonder if you would comment on the possible factors which led to his death?

DR. JOHN R. SMITH: When I saw this patient on his last admission, I was impressed with the possibility that he might have had acute rheumatic carditis in addition, of course, to severe cardiac failure.

DR. ALEXANDER: In other words, you

would postulate a recrudescence of acute rheumatic fever. Does the fact that he had no fever during the entire terminal illness mitigate against the diagnosis of acute carditis?

DR. SMITH: No, not necessarily; temperature elevation need not be present in acute rheumatic carditis.

DR. ALEXANDER: Very large doses of salicylate were given without effect. Yet it is still conceivable that the patient had acute rheumatic carditis; if so, would you expect the pathologist to demonstrate histologic evidence of the process?

DR. SMITH: Yes, I would.

DR. ALEXANDER: Are there other comments?

DR. HENRY A. SCHROEDER: On his third admission, the patient was found to have developed auricular fibrillation; it is conceivable that the onset of the arrhythmia precipitated the mild degree of cardiac failure noted at that time and which was controlled rapidly by the use of one of the digitalis glucosides.

DR. ALEXANDER: Do you believe that the occurrence of auricular fibrillation here constituted a manifestation of chronic rheumatic heart disease?

DR. SCHROEDER: Yes, I do, particularly in view of the excellent response to digitalis.

DR. ALEXANDER: Dr. Massie, do you have any further comment?

DR. MASSIE: I think the possibility that this patient had recurrent episodes of acute rheumatic carditis is suggested by the change in cardiac murmurs. Progressive failure *per se* should not have been accompanied by the appearance of an aortic diastolic murmur. One other possibility is that the patient continued to have bacterial endocarditis, in the abacterial phase described by Libman, although I believe such an explanation is highly unlikely.

DR. ALEXANDER: Are there any other factors which may have contributed to the patient's downhill course?

DR. C. V. MOORE: Concomitantly with the healing of vegetations, the degree of valvular deformity may actually be ac-

* MOORE, R. A., The cellular mechanism of recovery after treatment with penicillin. I. Subacute bacterial endocarditis. *J. Lab. & Clin. Med.*, 31: 1279, 1946.

centuated and may lead to progressive, intractable cardiac insufficiency.

DR. ALEXANDER: I believe a similar chain of events was reported by Libman in several of his patients who recovered from the disease.

DR. HARFORD: We have seen a number of our other patients, successfully treated for subacute bacterial endocarditis, subsequently develop rapidly increasing cardiac failure which ultimately led to death. Such a sequence constitutes a tragic sequel to the successful treatment of this disease which, until the introduction of penicillin, carried a mortality rate which approached 100 per cent.

DR. ALEXANDER: Is it possible that the patient did not receive enough digitalis? It is true that he probably would have died eventually of cardiac failure in any case but it was obviously desirable to achieve complete digitalization.

DR. ROBERT J. GLASER: As noted in the protocol, 0.3 mg. of digitoxin were given daily by the intravenous route in an attempt to slow the cardiac rate and decrease the pulse deficit. Because we had very little else to offer this man, we believed we were justified in giving large amounts and we believed adequate dosage was given; indeed, it seems probable that he actually received an excessive quantity.

DR. PALMER H. FUTCHER: The patient's non-protein nitrogen rose to a rather high level during his terminal illness. The rise, of course, may well have been a manifestation of hypochloremia and heart failure but, on the other hand, the patient had had scarlet fever and bacterial endocarditis, both of which may give rise to renal damage. I would therefore raise a question as to the possibility of glomerulonephritis.

DR. ALEXANDER: In summary, it seems clear that this patient, who had rheumatic fever at the age of six, developed subsequent rheumatic heart disease. At the age of twenty-two, he contracted subacute bacterial endocarditis which was apparently cured by a course of penicillin therapy. Subsequent to his recovery, recurrent car-

diac failure occurred and progressed, eventually failing to be controlled by all indicated measures and terminating in the patient's death. As possible explanations of the rapid downhill course following recovery from subacute bacterial endocarditis, several suggestions have been made; included, were acute rheumatic carditis and valvular damage secondary to the healing of bacterial endocarditis. Further valvular deformity from multiple attacks of rheumatic fever was also mentioned. As possible causes of azotemia, chronic glomerulonephritis or focal embolic nephritis were suggested.

Clinical Diagnoses: Rheumatic heart disease with mitral stenosis, mitral insufficiency and ? aortic insufficiency; cardiac insufficiency; subacute bacterial endocarditis, healed; ? acute rheumatic heart carditis; ? chronic glomerulonephritis or focal embolic glomerulonephritis.

PATHOLOGIC DISCUSSION

DR. OSCAR N. RAMBO: At autopsy, the body was that of a markedly emaciated man. There was marked edema of both lower extremities but no significant difference in the circumferences of the legs or thighs. Edema was also noted in the dependent portions of the upper extremities. On examination of the thorax, the most striking pathologic findings were in the heart. *In situ*, the apex was at the seventh rib in the mid-axillary line. The left transverse diameter measured 13 cm. and the right transverse diameter 7 cm. with a transthoracic diameter of 26 cm. The heart was globular in shape; there was marked dilatation of all chambers, particularly of the right atrium, right ventricle and pulmonary conus. There were no pericardial adhesions. The pericardial sac contained 200 cc. of dark yellow, cloudy fluid and in the epicardium of the right ventricle there was an irregular focal area of smooth fibrous thickening.

Internal examination of the heart showed dilatation and hypertrophy of the right atrium; the wall was 3 mm. thick. The tricuspid ring was dilated and the leaflets

were slightly thickened but not deformed. The wall of the right ventricle was 8 mm. thick. The left atrium was markedly dilated and its wall had an average thickness of 4 mm. In the endocardium of this chamber, there was a roughened, irregular area of yellow brown discoloration which lay inferior to the inferior pulmonary vein and superior to the posterior mitral leaflet. The mitral ring was slightly thickened, the leaflets showing diffuse fibrous thickening but no discrete nodules nor evidence of vegetations. The most significant change in the mitral valve was produced by thickening, shortening and fusion of the chordae tendinae. Diffuse areas of endocardial thickening of a smooth, white fibrous nature were found posterior to the mitral valve and inferior to the aortic valve. The left ventricle was markedly dilated; its wall measured 14 mm. in thickness. The cusps of the aortic valve showed only slight, smooth fibrous thickening, most marked at their bases, and there were adhesions between the cusps at the commissures. This process involved only 1 to 2 mm. of the free edges and produced only slight deformity. The coronary ostia and vessels showed no gross abnormalities.

The combined weight of the lungs was 1,220 Gm. Both were firm, dark and congested with moist, dark red, cut surfaces. In the periphery of the lower lobe of the left lung, there was a firm, dark red pyramidal lesion measuring 6 by 5 by 4 cm., the cut surface of which showed partial obliteration of the alveolar pattern. In the lingula of the upper lobe of the left lung and in the upper and lower lobes of the right lung, there were lobular foci of consolidation, greenish in color, measuring 2 to 10 cm. in diameter. No pleural adhesions were present.

In the abdominal cavity, the liver was remarkable in that it weighed only 1,050 Gm. It was dark brown with dark red foci in the centers of the lobules and was slightly firm in consistency. The spleen was enlarged, firm and dark red; it weighed 320 Gm. Near the hilus, a small subcapsular

triangular lesion measuring 6 by 5 by 4 mm. was found. It was yellow in color and fibrous in consistency. The kidneys were moderately enlarged, dark brown and firm with a few depressed scars, 2 to 5 mm. in their greatest dimension, on the cortical surfaces. The bladder was distended; its apex lay 7 cm. above the symphysis and it contained 800 cc. of dark yellow urine.

DR. ROBERT A. MOORE: This case presents interesting problems, both practical and theoretical, concerning whether or not the patient had subacute bacterial endocarditis and how the process was brought under control by penicillin two years before he died. In order to understand what has gone before, and before showing the microscopic sections, I would like to outline what appears to me to be the process of healing in bacterial endocarditis treated with penicillin and then to interpret the sequence in terms of this particular case. In a typical example of subacute bacterial endocarditis, there is a vegetation on the valve, the vegetation consisting anatomically of three parts. First, a central part which is necrotic, insofar as can be determined from looking at a microscopic section, next a layer of bacterial colonies and finally a thick layer of fibrin over the surface of the bacterial colonies, the layer of fibrin being approximately 500 to 750 micra in thickness. Similar vegetations form in the left auricular wall in the region that Dr. Rambo pointed out as being thickened in this case. Such vegetations characteristically are extremely small, very superficial and consist largely of bacterial colonies and a layer of fibrin; the vegetations which form on the left auricular wall do not have the large central necrotic core. There is instead a very small amount of necrotic material and the vegetations at this site characteristically never reach a large size. The healing process, insofar as can be determined, is as follows: the fibrous tissue grows up from the side and obliterates the layer of bacterial colonies and the layer of fibrin, forming a mass of fibrous tissue over the central necrotic mass. In several cases treated with penicillin which I have seen at

autopsy and in others reported from other laboratories, the central mass has undergone calcification. That is what Dr. Carl Moore had in mind when he pointed out that in the healing process of bacterial endocarditis, the valves may be further damaged to the point where the degree of valvular incompetence is actually increased; indeed, that is what happened clinically in most of the patients that have been reported so far in the pathologic literature.

When sections of the mitral valve of the patient under discussion were examined, there was only slight thickening and the thickening was uniform. The increase in size was caused partly by the thickening of the spongiosa on the auricular side of the valve and in part by the thickening of the fibrosa in the center of the valve. There was no significant change in the ventricularis on the ventricular side of the valve. The thickened valve did not show any swirling effects which are so frequently seen in the healing of both subacute bacterial endocarditis and rheumatic fever. It was the sort of valve that one would have expected to see in an individual who had had rheumatic fever as a child and had lived for ten or twenty years but not for thirty or forty years. Usually in a patient who dies at the age of thirty-five or forty and who had rheumatic fever in his youth, there is more thickening and many other manifestations, such as swirling in the connective tissue within the valve, rather than a uniform thickening which is characteristic of the earlier stages of valvular damage in rheumatic heart disease. I have no doubt, considering the history and the anatomic changes seen here, that this patient had rheumatic fever. I have serious doubt, however, that he had subacute bacterial endocarditis involving either the mitral or aortic valves although it is possible that he did. I have seen one example of subacute bacterial endocarditis in which the healing process did not leave the characteristic swirling or other deformity of the valve. In that case, I had always considered that the explanation of the absence of other changes lay in the

fact that the patient's endocarditis was due to a pneumococcus, an organism extremely sensitive to penicillin. Perhaps the organism in this case was likewise extremely sensitive so that the process was brought under rapid control and left very little evidence of valvular scarring. On the other hand, as I pointed out to you purposely, the vegetation from the left auricular wall is characteristically small and heals without a great deal of scarring. I therefore would postulate, on the basis of the history and findings, that this patient's subacute bacterial endocarditis was confined to the left auricular wall; it was brought under control rapidly and thus a large vegetation on the mitral or aortic valve never developed.

There are several other features which are highly characteristic of subacute bacterial endocarditis: (1) the presence of multiple small abscesses in the myocardium which are due actually to small infected infarcts; (2) larger infarcts in the spleen and kidneys and finally (3) as has been pointed out in the clinical discussion, focal embolic glomerulonephritis which is never seen except in connection with subacute bacterial endocarditis.

Let us now consider the evidence in favor of the diagnosis of subacute bacterial endocarditis in the present case. The first section (Fig. 1) is of the myocardium, showing a miliary infarct in which the muscle has been destroyed. There is a loose connective tissue remaining which is moderately well vascularized and some of the remaining myocardial fibers show advanced fatty degeneration. I doubt if this lesion goes back two years. It is more likely of several months' duration. We were unable to find any lesions in the myocardium which could be identified as so-called Brach-Wächter bodies. In Figure 2, a section of kidney is seen; a few glomeruli have been destroyed and replaced by adhesions. I think the evidence favors the fact that this patient probably had focal emboli glomerulonephritis sometime before his death. Further, Dr. Rambo described an infarct in the spleen, a section showing dense fibrous tissue of the type which one would expect to see in an infarct

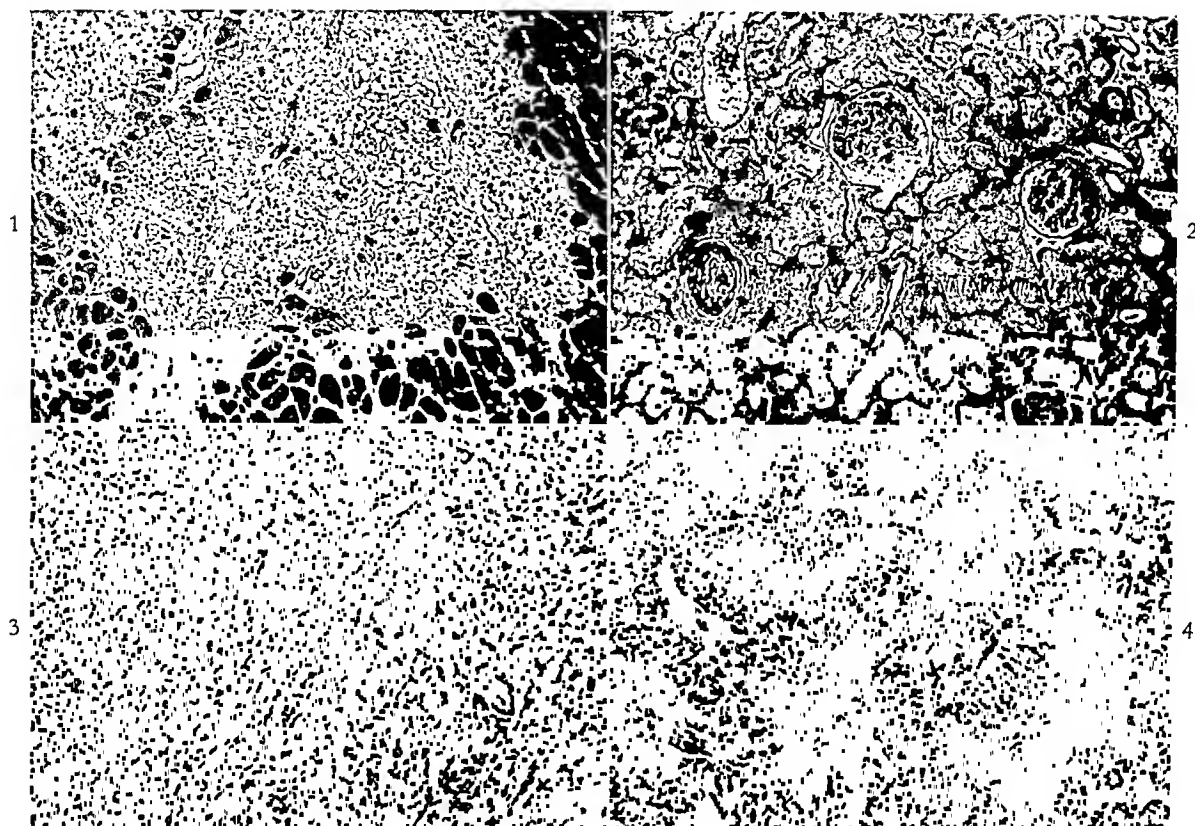


FIG. 1. Section of the myocardium showing a miliary infarct.

FIG. 2. Section of the kidney. Note that one glomerulus in this section has been destroyed.

FIG. 3. Section of the spleen showing the changes of advanced chronic passive congestion.

FIG. 4. Section of the liver again showing the changes of chronic passive congestion.

two years old. Thus, from these sections we can gather some evidence to support a diagnosis of subacute bacterial endocarditis.

The next two slides will illustrate the degree of chronic passive congestion. In Figure 3, a section of the spleen shows a characteristic glandular pattern with numerous large, dilated sinusoids lined by prominent cells, the so-called chronic spleen of advanced chronic passive congestion. In Figure 4, a section of the liver shows an advanced degree of chronic passive congestion. The regions have almost become confluent with the portal spaces isolated. The architectural pattern of the liver is reversed. This patient lost approximately one-half of his liver as a result of elevated venous pressure. In the sinusoids of the central regions there was also some proliferation of connective tissue. The lungs (Fig. 5) showed chronic passive congestion

and other findings as well. Pneumonia, thickening of the alveolar walls, proliferation of connective tissue and a fair amount of hemosiderin from chronic congestion can be seen. There is some suggestion of rheumatic pneumonia although this diagnosis cannot definitely be made. In Figure 6, another illustration of the change of the lung is seen.

A different section (Fig. 7) of the myocardium shows vacuolization of the fibers in the hematoxylin-eosin preparation and a fat stain (Fig. 8) demonstrates that this patient had a considerable degree of fatty metamorphosis of the myocardial fibers.

From these findings, it is clear that this patient had rheumatic heart disease and subacute bacterial endocarditis which probably involved the left auricular wall but not the aortic or mitral valves. The bacterial infection had been brought completely

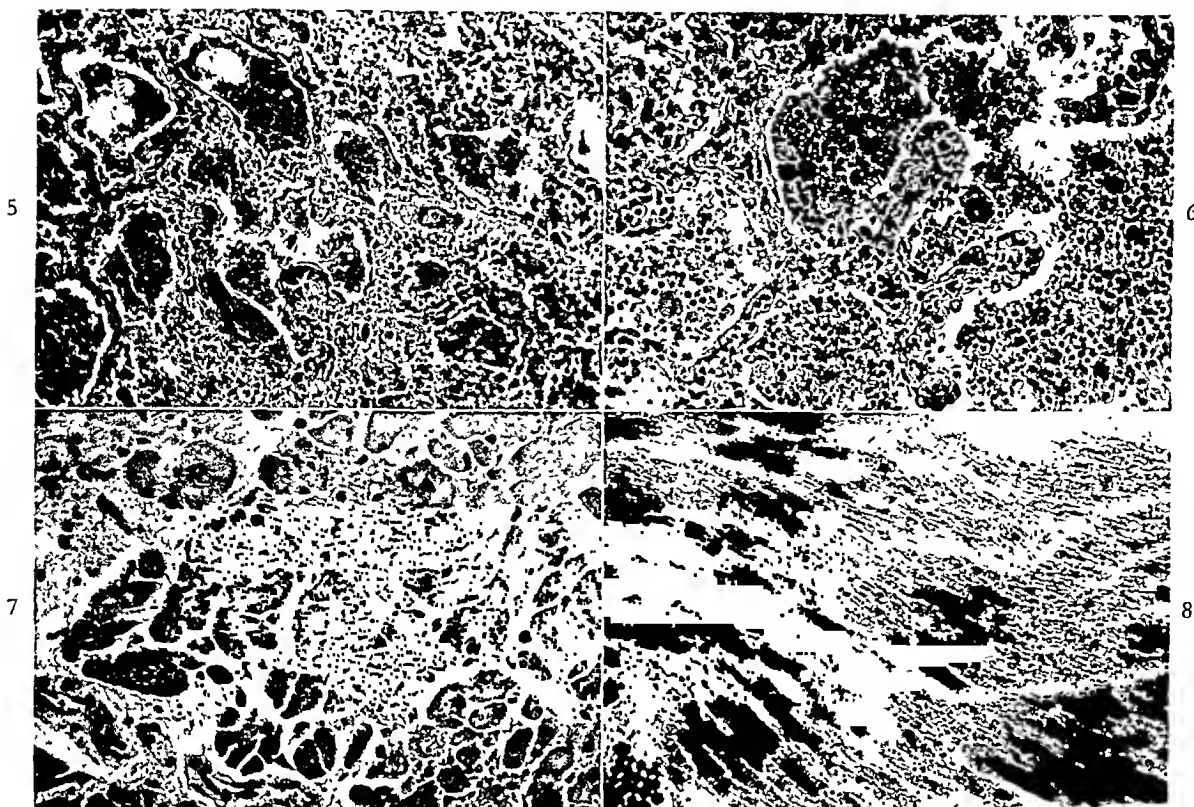


FIG. 5. Section of the lungs. The findings indicate both pneumonia and chronic passive congestion.

FIG. 6. Another section of the lung showing similar changes.

FIG. 7. Section of the myocardium showing vacuolization of the fibers. (H and E stain.)

FIG. 8. Section of myocardium stained for fat.

under control with a minimal amount of scarring. Then over a period of time, the heart failed and finally could not respond to treatment. No manifestations of acute rheumatic fever were noted. From an anatomic standpoint neither the mitral nor the aortic valves were damaged enough to explain the degree of hypertrophy and dilatation of the heart and it seems likely that at some earlier time, perhaps during the episode of subacute bacterial endocarditis, the patient suffered severe damage to the myocardium which caused the extensive dilatation and resulting hypertrophy. The patient finally succumbed, not of chronic

valvular disease, but because of myocardial disease *per se*.

Anatomic Diagnoses: Chronic endocarditis of the mitral valve, moderate, and aortic valve, slight; (clinical history of rheumatic fever, sixteen years, and treatment of subacute bacterial endocarditis with penicillin following tooth extraction two years ago); hypertrophy and dilatation of the heart (675 Gm.); hydropericardium (200 cc.); chronic passive congestion of the lungs, liver, kidneys and spleen; recent infarcts of the upper and lower lobes of the left lung; bronchial pneumonia of the upper lobe of the left lung and upper and lower lobes of the right lung.

Case Report

Infectious Mononucleosis with Severe Central Nervous System Involvement

WILLIAM W. FIELD, M.D.

New York, New York

CASES of infectious mononucleosis exhibiting signs of central nervous system involvement have from time to time been reported in the literature. Bernstein in his comprehensive review of the disease says that central nervous system involvement is occasionally encountered and that when it is, "the commonest initial symptoms in this form of the disease are headache, signs of meningeal irritation and blurring of vision. In certain instances there have been convulsions, stupor and coma."

In the majority of these patients signs of meningeal irritation have outweighed other central nervous system findings. Many have reported headache, positive Brudzinski and Kernig signs and an increase in the total lymphocyte count in the spinal fluid. In 1931, Epstein and Dameshek reported a case of a nineteen year old Russian-Jewish male who developed headache, blurring of vision and stupor. Lymphadenopathy and splenomegaly were present and lymphocytosis with atypical cells was reported. Subsequently, the patient developed a positive Brudzinski sign. There was a moderate increase of cells in the spinal fluid.

In 1941, Landes, Reich and Perlow reviewed the subject of central nervous system involvement in infectious mononucleosis and concluded that neurologic signs may be multiple: headache, photophobia, nystagmus, poor articulation, nausea and vomiting and positive Kernig and Brudzinski signs. Spinal fluid findings may also vary, the pressure

may or may not be elevated. Pleocytosis may vary from 25 to 300 cells, the majority being lymphocytes. The spinal fluid protein may be increased as well as the globulin fraction. Their patient was admitted with headache, dizziness, vomiting and a staggering gait. The blood smears were typical of infectious mononucleosis but the lymphadenopathy and splenomegaly did not appear for three weeks after onset of the disease. Eleven days after onset the heterophil antibody test became positive, 1 to 1,024. The total protein of the spinal fluid was elevated without cellular increase.

In 1934, Hiller and Fox reported a case of infectious neuronitis complicating infectious mononucleosis. This patient developed lymphadenopathy, splenomegaly, a heterophil antibody test positive to 1 to 125 and subsequently, a motor paralysis of the lower extremities of an ascending type. The spinal fluid contained markedly elevated protein with no increase in the cell count. The authors believed that the entire picture could be explained on the basis of infectious mononucleosis complicated by the Guillain-Barré syndrome.

The case presented here developed the clinical picture of infectious mononucleosis; the patient had typical blood smears and positive heterophil antibody tests. He developed signs of severe central nervous system involvement with markedly elevated spinal fluid protein and only a modest increase in cells.

CASE REPORT

A nineteen year old white, male soldier was admitted to the medical service on March 30, 1946, with complaints of weakness and a slight headache beginning two days before entry. The night before admission the patient became dizzy when walking to the latrine and almost fainted. Examination upon admission revealed a well developed young male with no positive physical findings other than a mild follicular tonsillitis and an enlarged cervical lymph gland at the angle of the mandible on the right side.

The second day after admission the patient got up to shave and was seen to stagger. Suddenly he fell to the floor, making wide purposeless movements of his limbs. When seen by a medical officer ten minutes later he was unresponsive, making aimless motions with his limbs. Blood ran from a corner of his mouth. Urinary and fecal incontinence were present. The pupils were widely dilated and failed to respond to light. Discs were normal, no nuchal rigidity was found. All reflexes were hyperactive and bilateral ankle clonus was noted. No Babinski reflex was elicited. Blood pressure was 112/?, temperature 101°F., respiration was not labored and the pulse was rapid but of good quality. He showed poor response to sedation and a lumbar puncture was performed under the most trying conditions. The spinal fluid was clear and did not appear to be under increased pressure but accurate pressure readings could not be obtained because the patient was thrashing around so violently. Immediately after the seizure, blood was drawn for analysis and revealed blood sugar 100 mg. per cent and blood calcium 11.3 mg. per cent. Examination of the spinal fluid (Table III), revealed no increase in the cell count but markedly elevated total protein, 340 mg. per cent, moderately elevated sugar, 93 mg. per cent and chlorides, 800 mg. per cent. Culture of the spinal fluid was subsequently reported negative. At this time the diagnoses considered were: epilepsy, intracranial hemorrhage, intracranial tumor, and in view of the albuminocytologic dissociation, Guillain-Barré syndrome although it was unlikely in view of the rapid onset with convulsions.

The following morning the patient's temperature went to 103.6°F., and he showed

marked nuchal rigidity and positive Brudzinski's and Kernig signs. He was still comatose and restless; his reflexes remained unchanged. At this point the diagnosis was encephalitis, cause unknown and he was transferred to the contagious service. The white blood count was

TABLE I
WHITE BLOOD COUNT

Date	April 2	April 6	April 15
Total count	18,000	11,500	11,150
Polymorphonuclears	40%	32%	57%
Lymphocytes	60%	68%	43%
Morphology	many atypical lymphocytes	many atypical lymphocytes	normal

reported as 18,000, polymorphonuclears 40 per cent and lymphocytes 60 per cent. (Table I.) The differential smear showed many atypical lymphocytes, a large number having deeply basophilic cytoplasm, vacuolated with a foamy appearance. Many cells were fragmented. The nuclei were round, oval or indented, staining

TABLE II
HETEROPHIL ANTIBODY TESTS

Date	Dilution
April 3.	1-1792
April 6.	1-448
April 9	1-896
April 15.	1-224
April 25	1-112
April 30.	1-56
May 20.	negative

deeply and occasionally fenestrated. On the strength of the presence of these atypical forms, a heterophil antibody test was done and the following day reported positive through 1 to 1,792 dilution. (Table II.) Lumbar puncture this day revealed 96 cells (62 lymphocytes, 34 polymorphonuclears), total protein 320 mg. per cent, a negative culture and a negative spinal fluid Wassermann.

On April 4th, the patient, still remaining comatose, restless and unresponsive, developed a right hemiplegia with paralysis of the right face of the peripheral type. Conjugate deviation of the eyes to the left was noted. Nystagmus was present with the quick component to the left. Reflexes on the right side became markedly hyperactive, a Babinski's sign appeared as well as a suggestive Hoffman's sign. Reflexes on the left side were sluggish. A grasp reflex was present in the left hand and strength remained

good on the whole left side of the body. A homonymous hemianopia was present on the right side and sensation was definitely diminished on the right, or paralyzed side of the body. Speech was incoherent and represented a motor aphasia.

constantly been to the right. Periods of apnea developed and became more marked and prolonged.

April 8th, marked the peak in the course of the disease. Upon examination the eyes were now seen to deviate to the right; the right

TABLE III
CEREBROSPINAL FLUID ANALYSES

Date.....	April 1	April 3	April 6	April 8	April 15	April 30
Appearance.....	clear	clear	clear	clear	clear	clear
Cells.....	normal	96 (162, P 34)	9 lymphs	248 (1230, P 18)	normal	normal
Protein.....	340 mg. %	320 mg. %	240 mg. %	216 mg. %	163 mg. %	39 mg. %
Sugar.....	93 mg. %	77 mg. %	60 mg. %	54 mg. %		
Chlorides.....	800 mg. %		600 mg. %	600 mg. %	660 mg. %	
Culture.....	negative	negative	negative			
Wassermann.....		negative				

By April 6th, the patient was more quiet and the purposeless movements were fewer, but the aphasia and hemiplegia remained unchanged. A Kahn test was reported negative. Lumbar puncture was repeated this day and normal pressure readings were obtained. Initial pressure 165 mm. of water. Spinal fluid findings were: clear fluid, 9 cells (all lymphocytes) and total protein 240 mg. per cent. The white blood count was 11,500, lymphocytes 68 per cent, polymorphonuclears 32 per cent and it again showed many atypical forms.

At midnight on April 7th, the patient suddenly went into a convulsion; there were clonic movements of all the limbs and twitchings of the facial musculature. Breathing became stertorous and rapid and he vomited large amounts of brownish fluid. Some of the vomitus was aspirated and suction via nasal catheter was carried out immediately. Respirations remained noisy and trismus was marked. Three hours later the patient convulsed again. Jacksonian movements of the jaw and facial muscles predominated. During this time he was incontinent and the pulse varied widely from 48 to 128 per minute. At 0500 hours the next morning respirations became Cheyne-Stokes in type. It was noted that at this time during the convulsions the ocular deviation was to the left, whereas for the preceding days of illness deviation had

homonymous hemianopia was still present. In addition to the right hemiplegia, the left side was now paralyzed and reflexes on the left had now become hyperactive. However, no Babinski reflex was elicited on the left. The aphasia remained pronounced. The periods of apnea in Cheyne-Stokes respiration were alarming, coma seemed more profound than at any previous time and recovery appeared doubtful.

Thereafter, the patient began to improve. The fever which had previously run 100° to 103°F. fell gradually to reach normal on April 11th. Pulse and respirations levelled off. By April 10th, response to painful stimuli was definite on the right side and the left arm moved impulsively. On April 11th, the eyes were moving freely in all directions with no dissociation and vision was apparently returning to the right eye. Speech remained affected and only a few words could be made out. On April 15th, the patient got out of bed unassisted. On the same day the heterophil antibody test had fallen to 1 to 225 and in the blood smear the normal ratio of polymorphonuclears to lymphocytes had returned. Two nights later and for several nights to follow, he apparently had hallucinations while asleep, crying out and seeing objects run across the ceiling. By April 22nd, these had disappeared and a slight speech impediment,

in addition to memory defects, were all that remained.

Examination on May 14th, revealed no positive physical findings and the neurologic examination was negative. All laboratory tests had returned to normal. The boy had some difficulty recalling parts of his army career and he tired readily; otherwise, he felt well. On May 26th, the patient was discharged from the hospital on convalescent furlough.

In this patient the onset of the central nervous system involvement followed within two days the development of tonsillitis and lymphadenopathy. Two days following this the heterophil antibody test was strongly positive, blood smears were typical and the spinal fluid protein was markedly elevated. The almost simultaneous onset of these symptoms and signs would seem to indicate that only one disease was present and that the disease was capable of protean manifestations. In view of the history, the clinical findings and the blood picture it is

logical to explain all the manifestations as due to infectious mononucleosis.

SUMMARY

A case is presented of infectious mononucleosis with severe central nervous system involvement as evidenced by transitory paralyses, right homonymous hemianopia and marked rise in spinal fluid protein. Subsequently, all clinical signs and laboratory data returned to normal.

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166 E. 96 St.

Book Review

An Integrated Practice of Medicine. By Harold Thomas Hyman, M.D. Volumes I, II, III and IV and Index. Pp. 4,131, with 1,184 illustrations, 305 in color. Philadelphia, 1947. W. B. Saunders Company. Price \$50.00 per set.

"An Integrated Practice of Medicine" is an effort to present in four volumes a complete textbook for the general practitioner. Omitting only elective major surgery, in the words of the author it "supplements the material of internal medicine with authoritative text devoted to the clinical subjects of Infection, Tropical Medicine, Allergy, Metabolic Disorders, Poisonings, Toxicology, Neoplastic Disease, Cardiology, Hematology, Endocrinology, Psychiatry, Neurology, Ophthalmology, Dentistry, Dental Surgery, Gastro-Enterology, Proctology, Otology, Rhinology, Urology, Gynecology, Obstetrics, Pediatrics, Orthopedics, Dermatology, Minor Surgery, Anesthesiology, Emergency Surgery, Convalescence and Rehabilitation. It includes brief but complete and accurate surveys of the pre-clinical sciences of Anatomy, Serology, Immunology and Physiological Chemistry, as well as meticulous details of the practical clinical disciplines of Physical Diagnosis, Laboratory Methods, Clinical Pathology, Pathologic Physiology, Electrocardiography, Dietetics, Radiology, Prognosis, Pharmacology and Therapeutics."

Obviously, to attempt to place so much material within the confines of approximately four thousand pages is an ambitious undertaking. It is noteworthy that the author and his various specialist associate editors have been able to accomplish their purpose so well. From the viewpoint of the general practitioner requiring brief discussions often seasoned with the author's advice, or wishing to refresh his memory quickly on a wide variety of topics, this book should be of great value. On the other

hand, it should be emphasized that this is no reference work and is in no way comparable to one of the authoritative systems of medicine.

The work is divided into twenty-five sections, each of which covers some general field, such as infection, allergy, pediatrics or the respiratory system, and many of which have been written with the aid of a more specialized associate editor. Each section is then broken down into chapters discussing in turn specific topics. When possible the presentation follows the pattern: etiology, epidemiology, pathology, clinical manifestations, course, diagnosis, complications, prognosis, active treatment, preventive treatment and occasional special leads, e.g., in rheumatic fever, marriage and pregnancy, and surgery in cases of rheumatism.

The composition is exceptionally readable, ordinarily factual even if sometimes commonplace, and given to practical detail; it is scattered with the author's opinions, and considerably helped by frequent cross references. Some 319 tables of differential diagnosis are included. It may be noted that brevity of presentation frequently interferes with completeness but on the whole an amazing amount of practical though general information is given. Each volume contains its individual index and in addition a separate full index volume aids in the quick location of topics. The text is studded with really first class illustrations. The volumes are well bound and printed and are not so large or heavy as to be unwieldy. A selected bibliography for physicians resident in small towns or cities without library facilities is given.

For the general practitioner, for whom this work is primarily intended, the author and his colleagues have done an excellent job.

F. K. H.

Editorial

The Antibiotic Age

EVER since the convincing studies of Colebrook and Kenny¹ on the effectiveness of prontosil in the treatment of puerperal infections and the significant results obtained by Chain, Florey and their associates² following the administration of preparations of penicillin to patients with severe staphylococcal and streptococcal infections, chemotherapy and antibiotic therapy have emerged from the experimental stage; and their use in all types of infection to which man is susceptible has dominated clinical medical practice and its literature. It has been an exciting era that has seen a drop in the mortality of so serious and common a disease as pneumococcal pneumonia from 25 or 30 per cent to a probable irreducible minimum of 2 to 3 per cent; deaths from bacterial endocarditis and several forms of meningitis are reduced from 100 to 25 per cent with prospects of going lower; the management of surgical complications either threatened by or accompanying ruptured and diseased viscera is immeasurably simplified; the potentialities that were formerly contained in the possible explosion of initial local

infections such as acute tonsillitis or otitis media into serious extensions of suppuration—angina, septicemia, mastoiditis, meningitis—are almost eliminated; the duration of the morbidity of innumerable non-fatal infections has been reduced in some instances to a matter of hours. Since bacterial infections of one kind or another make up such a considerable proportion of the organic ills of man, it is readily understandable that the practical uses of chemo- and antibiotic therapy should be explored to the greatest degree and that published reports of their successes and limitations should fill medical journals in the most conspicuous fashion.

That these preparations have a therapeutic value of magnificent proportions is now an established fact. It is, therefore, pertinent and of considerable interest to broaden clinical medical thought concerning antibiotics to include other phases of the subject, to consider in addition to curative effects other elements of medical importance that are developing in association with the extraordinarily widespread use of sulfonamides and penicillin, as well as newer reagents of fungal origin such as streptomycin and still others to come. It is the purpose of this article to outline some of the phases of medicine that are changing under the impact of antibiotic therapy.

One could elaborate at considerable length on the effect which this form of pan-treatment is having in substantially modifying the picture of the clinical course

¹ COLEBROOK, L. and KENNY, M. Treatment with prontosil of human puerperal infections due to haemolytic streptococci. *Lancet*, 1: 1279, 1936; *Lancet*, 2: 1319, 1936.

² (a) CHAIN, E., FLOREY, H. W., GARDNER, A. C., HEATLEY, N. G., JENNINGS, M. A., ORR-EWING, J. and SANDERS, A. G. Penicillin as a chemotherapeutic. *Lancet*, 2: 226, 1940. (b) ABRAHAM, E. P., GARDNER, A. C., CHAIN, E., HEATLEY, N. G., FLETCHER, C. M., JENNINGS, M. A. and FLOREY, H. W. Further observations on penicillin. *Lancet*, 2: 177, 1941.

of disease from the classical descriptions of former years, or in re-orienting points of emphasis in pathologic physiology as new aspects of disease become more apparent and relatively more significant, or in altering the morphologic pathology of inflammation in some instances and affecting the processes of repair in others. It is sufficient, however, for the purposes of this review to illustrate with a few selected examples the subject matter to which attention is invited.

As an example of the first point, namely, changing clinical pictures, pneumonia may be cited. At the present time the classical bacterial pneumonias when treated at home rarely require institutional care, and, if hospitalized, usually recover within the first twenty-four hours after admission. The greater portion of the population of protracted acute pulmonary infections is therefore now made up largely of numerous forms of suppurative and non-suppurative pneumonitis that are not amenable to antibiotic therapy. Their etiologies and pathogeneses are obscure and their clinical pictures are not well defined. For this reason they have become the most conspicuous type of acute pulmonary infections presented for discussion and study, and as a result the classical course of the rapidly cured lobar pneumonia has become for the younger generations a subject of historic interest only. This same type of change is evident in many other internal medical diseases, as well as in those encountered among the surgical and non-surgical specialties.

The veering of emphasis which has resulted from antibiotic therapy may be seen in surgical management in which patients are well saturated with antibacterial reagents before, during and after operative procedures. Since the hazards of infection are either eliminated entirely or rendered less likely, interest now centers around elements in technic that promote the maintenance of normal functional activity in spite of surgical alterations, and in minimizing the cellular and tissue damage that is an unavoidable part of surgical incisions and visceral manipulation. Factors that concern

the formation of postoperative adhesions must be restudied from the point of view of the effect of antibiotic therapy on the processes of tissue repair in an antibacterial surgical field.

In the field of pathology of inflammation, bacterial endocarditis may be mentioned briefly as an illustration. One of the common findings now noted at autopsy in such patients treated extensively with penicillin is either ruptured chorda tendinae or fenestrated valves. Formerly these abnormalities were rare. There is some evidence that the processes of repair in diseased valves in which the infection is either obliterated or severely restricted by penicillin are not characterized by the extensive thickening of fibrous replacement. This course of events plus the increased span of life of patients with endocarditis constitute a set of circumstances that contribute to the development of newer aspects of disorders arising from the effects of antibiotic therapy.

The discussion may be taken one step further. In viewing the antibiotic age, perhaps greater interest, even if of a more speculative nature, centers around whether or not the present day satisfaction with the success of antibacterial therapy can be transformed into a permanent optimism for generations to come. For an elaboration of this problem it is useful to consider the situation from the point of view of the bacteria themselves. These microscopic forms of viable protoplasm must be viewed with an inordinate degree of alarm the profound threat to their survival that has arisen. The situation to them is of the same magnitude as the age of the atomic bomb is to the human species.

In their common dilemma of possible annihilation, men are at the moment utilizing intellectual forces to meet the danger of extinction, while microbes are calling biologic laws into play. In the latter field, well established Darwinian principles are being invoked that determine the origin of new species and the survival of the fittest. Such processes offer to the pathogenic

bacterial species the possibility that new characteristics may emerge among strains of their population to make survival and multiplication possible in the universal antibiotic environment in which they find themselves. That events of this nature are actually happening is seen both in clinical experience in which patients are encountered whose infection is refractory to an otherwise successful form of specific treatment and in the laboratory where bacterial variants and mutants possessed of drug-resistant properties are being identified. The biologic processes involved are of immense practical clinical importance and warrant the interest of all fields of medical activity.

Although knowledge of the subject is incomplete, current information indicates that two forms of resistant strains of pathogenic micro-organisms may be encountered; the one the so-called "naturally resistant" strains, the other consisting of strains that have "acquired" resistance. A conspicuous example of the first type is found in patients who from the beginning of treatment fail to respond and from whom the strain initially isolated is found by laboratory tests to be unharmed by antibiotic substances. The second type is encountered in patients who temporarily improve under treatment and from whom cultures of the initial infecting strain are found to be susceptible to antibiotic action but who, when relapse occurs, yield cultures that are capable of multiplying in the presence of large amounts of the therapeutic reagent. The existence of naturally resistant individual strains among any bacterial species, grouped as being sensitive to antibiotics, appears to be dependent upon the fact that the cells of the particular strain have perhaps always possessed and passed on to successive generations natural properties that endowed them with this special resistance although these potentialities had never previously been realized by the bacteria nor recognized in laboratories. They represent an example of the wide variation in biologic characteristics among free-living cells based on the chance distribution of genes throughout

succeeding generations. In this particular instance, by happenstance, the biologic characteristic transmitted by some gene or other defies the untoward effect of the sulfonamides, penicillin or streptomycin. The persistence of such infecting strains and the diseases which they produce are assured until some new antibiotic substance to which they are vulnerable becomes available.

Another instance of the occurrence of strains possessing initial resistance has been found in patients whose infection was derived by transmission from other patients or carriers also infected with resistant strains, in some cases of the naturally resistant type and in others created by previous treatment.

The development in patients of strains with "acquired resistance" appears to be dependent upon the classical laws of natural selection. The universal clinical practice of treating essentially all patients with specific antibacterial therapy forms ideal circumstances under which the laws of evolution and the survival of the fittest may operate. Since millions of generations of bacteria may be observed in a relatively short period of time, the elimination of the "unfit" bacteria and the retention of the drug-resistant forms is proceeding rapidly at the present time. That such a sequence of events does actually occur in disease was most clearly demonstrated in cases of gonorrhea occurring in the Armed Forces during World War II. The effective response to treatment with sulfonamides dropped in a few years time from an initially high success to a proportionately small number of cures. The failures were to a great degree directly referable to the presence in the infected population of sulfonamide-resistant strains. Fortunately, at about this time penicillin became available to meet the therapeutic problem successfully, and neisseria have not yet exhibited the capacity to resist its antibiotic action.

Still another point of special interest from a genetic and biologic point of view is found in the recent provocative reports of

Miller and Bohnoff.³ Briefly stated, they found that among strains of meningococci some of the cells were resistant to the antibiotic effect of streptomycin. When the transfer of colonies growing on media containing streptomycin was attempted, it was found that some of them grew by subculture on other media containing streptomycin but actually failed to multiply in streptomycin-free media. Under these circumstances it appears that streptomycin, instead of being a harmful reagent, proved to be a necessary accessory nutrient factor. This finding *in vitro* was made additionally interesting by the experiments performed *in vivo* in which mice survived infection with the special strains; but if the animals were "treated" with streptomycin they died, presumably because under the latter circumstance the organisms could grow in the body more luxuriantly if streptomycin was present. In this particular experimental instance the bacteria appear to have reached the height of biologic ingenuity in that they not only did not find themselves damaged by the antibiotic reagent but utilized it for

purposes of multiplication and growth. The potential implications of this circumstance for the future of antibiotic therapy are obvious. Its confirmation and further elaboration are matters of considerable importance.

There are other aspects to the problems of bacterial behavior which are of necessity omitted. A pertinent factor lies in the extent to which bacterial species are capable of utilizing the biologic laws at their disposal. They may fail. Darwin in "The Origin of the Species" has expressed this principle as follows: "Though nature grants long periods of time for the work of natural selection, she does not grant an indefinite period; for as all organic beings are striving to seize on each place in the economy of nature, if any one species does not become modified and improved in a corresponding degree with its competitors, it will be exterminated. Unless favourable variations be inherited by some at least of the offspring nothing can be effected by natural selection." It appears that this phase of the fundamental principle will have a most important bearing on the future status of the effectiveness of clinical antibiotic therapeutics.

WILLIAM S. TILLET, M.D.

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Observations on a Normal Young Woman Given Synthetic 11-Dehydro- corticosterone Acetate*

F. HOMBURGER, M.D., J. C. ABELS, M.D.† and N. F. YOUNG, Ph.D.

New York, New York

THIS report deals with the effects of synthetically prepared 11-dehydrocorticosterone acetate (Compound A of Kendall, DHCA) in a normal female. Hitherto compounds of this type formed by the adrenal cortex have been investigated principally for their action in experimental animals and in patients with pre-existing endocrine disorders, including Addison's disease.

The possible general significance of the physiological disturbances shown by patients with Cushing's disease and allied conditions makes important any information on the action of pure compounds formed by the adrenal cortex. The demonstration by Dobriner and his associates¹ of abnormal steroids probably of adrenal origin in the urine of patients with cancer and other disorders warrants further precise study of the action of pure substances of adrenal origin.

The effects of 11-dehydrocorticosterone in animals have been reviewed by Ingle² and may be summarized by the statement that this substance increases working capacity, glycogenesis and sodium retention in adrenalectomized rats and prolongs their survival.

Perera, Blood and Reinhold³ have studied the effects of 20 to 100 mg. of 11-dehydrocorticosterone acetate in two patients with Addison's disease and in one subject with hypoadrenalism secondary to anterior pituitary insufficiency. A slight retention of salt and water was observed at the higher dosage levels, whereas carbohydrate and nitrogen metabolism were not affected; no alterations were found in any of the other functions measured. Forsham, Thorn, Bergner and Emerson⁴ studied the response of fourteen patients who had Addison's disease and of one normal subject to doses of 11-dehydrocorticosterone acetate varying from 10 to 60 mg. daily and concluded that "a decrease in sodium excretion occurred in 13 to 14 experiments and a decrease of chloride excretion was observed in all . . . An increased renal excretion of total nitrogen was observed in 12, of potassium in 11 and of inorganic phosphorus in 9. Uric acid excretion was increased in 13 out of 14 experiments. The percent increase in uric acid nitrogen was approximately twice as great as the increase in total nitrogen. Alpha amino acid nitrogen excretion increased significantly during Compound A therapy in the two experiments in

* From the Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. This work was aided by grants from the National Cancer Institute and the Teagle Foundations, Inc., and was carried out with the technical assistance of Vera Collier and Josephine Green.

† Deceased June 13, 1947.

which it was determined. During Compound A therapy fecal fat was decreased by 60% in 3 patients in whom it was studied, fecal nitrogen loss was decreased by 37% in one case with a similar decrease in wet weight. . . . In one patient 60 mg. of Compound A daily was followed by a distinctly higher glucose tolerance curve. . . . In a normal male subject maintained on a constant diet the administration of Compound A was associated with increased sodium and chloride retention. . . . There was a significant increase in urinary output of nitrogen, uric acid, potassium and inorganic phosphorus with a fall in sodium excretion." The changes on which these conclusions are based seem in many instances close to the borderline of significance.

It was also found that Compound A exerted a consistent effect in preventing hypoglycemic symptoms in patients with Addison's disease during a prolonged fast or when maintained on a low carbohydrate, high protein and high fat diet.

Sprague, Gastineau and Power⁵ using 50 to 200 mg. of 11-dehydrocorticosterone acetate in a patient with Addison's disease found a mild and delayed retention of sodium chloride and water at the higher dosage level and little or no change in the glucose and insulin tolerance tests (with the exception that hypoglycemia was better tolerated). The blood sugar was better sustained during prolonged fasting when the hormone was given. Changes in the levels of the fasting blood sugar during administration of 11-dehydrocorticosterone acetate, however, were small and probably not significant. There was a moderate increase in 11-oxysteroid (cortin-like) substances in the urine while the compound was being given.

Sprague, Kepler and Power⁶ studied the effects of naturally occurring 11-dehydrocorticosterone in three patients with Addi-

son's disease and diabetes mellitus. Doses from 16 to 100 mg. were employed and the effects were studied by measuring the patient's excretion of glucose, nitrogen, ketones, sodium and chloride, and the changes in the level of the blood sugar during a twenty-four-hour fast following the withdrawal of insulin. The changes found were not impressive and may be summarized in the statement that 11-dehydrocorticosterone in the doses employed did not have a very potent effect on either electrolyte or carbohydrate metabolism in these patients.

In this communication studies are reported of several metabolic functions before, during and after the administration of 200 to 400 mg. per day of 11-dehydrocorticosterone acetate in oil to a normal woman thirty years of age. The results of this study showed that DHCA caused a mild retention of sodium and water, and had no immediate effect on the carbohydrate metabolism during forty-eight-hour fasts. There were delayed effects on the carbohydrate metabolism which could not clearly be attributed to the compound. DHCA did not change the excretion of 17-ketosteroids in the urine.

CASE REPORT

The subject used for this investigation was a white woman thirty years of age who sought medical attention six months before this reported study with complaints of premenstrual mastodynia, fatigue, nervousness and cancerophobia. She was eager to avail herself of a prolonged period of hospitalization to rule out organic disease and test the effects of certain hormones.

Physical examination was essentially negative and did not reveal any stigmata of endocrine disorder.

Routine laboratory examination including urea clearance and urine concentration and dilution tests were normal. (Table 1.)

All data indicated that the subject was physi-

eally normal but psychoneurotic and she was admitted for metabolic study. The course in the hospital was uneventful; the patient was most cooperative.

An adequate and palatable diet was composed to suit the taste of the patient and contained

During the first six days of this period the salt intake was restricted to about 2 Gm./day. Thereafter, during this period 1 ml. of normal saline solution and 1 ml. of benzyl benzoate in benzyl alcohol were administered intramuscularly on several occasions to accustom the patient

TABLE I
BLOOD ANALYSES

Date	Hr	Remarks	Total Protein, Falling Drop Method	Total Protein, Gm/100 ml Kjeldahl	NPN, mg/100 ml	Urea, N, mg/100 ml	Proteose N, mg/100 ml	Amino N	Chlorides, mEq/liter	Na, mEq/liter	K, mEq/liter	Phosphorus Inorg, mg/100 ml	Calcium, mg/100 ml	CO ₂ Combining Power, mEq/liter	Cholesterol, Tot mg/100 ml	Blood Sugar		Uric Acid, mg/100 ml
																Date	mg/100 ml	
5 8	8 AM	Control period	7 1	6 53	24 4		1 1	4 23	104	139 2	4 4	2 48	11	24 8		5 9	98	
5 10	9 AM					14 5										5 10	124	
5 15	8 AM		6 7	6 73	19 5		3 3	3 60	105	137 8	4 3	3 5	10 2	24 8		5 16	114	
5 22	8 AM		6 4	6 27	22 8		6 6	4 88	103	137 8	4 5	3 12	10 2	25 2		5 17	118	
5 29	8 AM			5 85	23 6	11 3	4 3	5 12	106	137 8	4 0	3 32	10 3	26 0		5 23	112	
6 6	9 AM	Fast (6 5-6 7)			21 5	7 0	3 8	4 47	105	137 8	4 4	3 62	10 5				91	3 4
6 6	3 PM	plus 11-DHCA* (6 5-6 10)			15 5	5 3	1 7	4 23	108	140 6	4 4	3 46	10 5				103	3 4
6 6	9 PM				16 7	6 1	1 7	4 5	103	139 2	4 8	3 14	10 0				110 5	3 4
6 7	3 AM				19 7	7 7	0 9	4 5	104	139 2	4 6	3 64	10 0				117 3	4 0
6 7	9 AM				20	7 7	5 0	4 2	108	138 4	4 3	3 26	10 0				105	4 2
6 7	3 PM				21	11 0	0	2 99	101	134 4	4 2	2 6	9 6					3 6
6 11		Day after 11-DHCA		5 42	20 3		2 3	4 5	110	137 8	4 2	2 9	9 9	26 8	255		91	3 6
6 19	9 AM	Fast	7 3		20 4	7 2	1 6	3 46	111	137 8	4 2						80 5	3 6
6 19	9 PM					6 7	3 35		104	137 8	7 2	3 48	10 6				80 6	3 6
6 20	9 AM				20 8	8 8	8 5	4 26	104	137 8	4 3	3 38	10 4				77	4 5
6 25	9 AM	Between fasts		6 96											223		149	
6 26	9 AM							3 98		141	4 3						96	
6 27	8 AM		7 3	6 24		9 1			108	140	4	2 86	10 6	24 4			117	3 2
7 10	9 AM	After fast		6 0		11 8		4 82	105			3 2	10 1	20 4	220		93	5 4
7 18	9 AM	Before discharge	6 8	6 83		10 2			109			3 1	10 3	17 2	211	7 17	117	3 8

* 11 DHCA = 11-Dehydrocorticosterone acetate

per day carbohydrate 310 Gm.; protein 70 Gm.; fat 95 Gm.; NaCl 112 to 120 mM; total potassium 90 to 118 mM. The diet was prepared from the same stock of frozen meat and vegetables throughout the experiment and repeatedly analyzed for Na, Cl, K, N and fat. Two and a half liters of water (diet plus drinking water) were taken daily. Additional NaCl in weighed amount was given from a salt shaker as the experiment required.

The patient lived in the hospital on a fixed regimen of rest and activity, remained in bed until 10 A.M., retired at 8 P.M. and walked for two hours in the afternoon.

A preliminary period of twenty-four days was allowed during which the initial tests were done.

to injections and so avoid the subjective reactions of fear in the course of the experiment. A first forty-eight hour fast was then instituted during which only water was given. As soon as the glucose tolerance had returned to normal a second forty-eight hour fast was started and the injection of 11-dehydrocorticosterone acetate was begun.

The fast was repeated again following the return of glucose tolerance curves to normal levels and repeated once more toward the end of the experiment. Throughout the study blood was taken repeatedly for electrophoretic studies of plasma, and for determinations of the plasma volume, extracellular water and of those constituents recorded in Table I.

Complete hematological studies were made every two or three days. The daily blood pressure readings were taken by the same physician at the same time before the patient was weighed.

DHCA administration. Daily vaginal smears were obtained following the administration.

Glucose tolerance and insulin sensitivity were measured repeatedly during the control

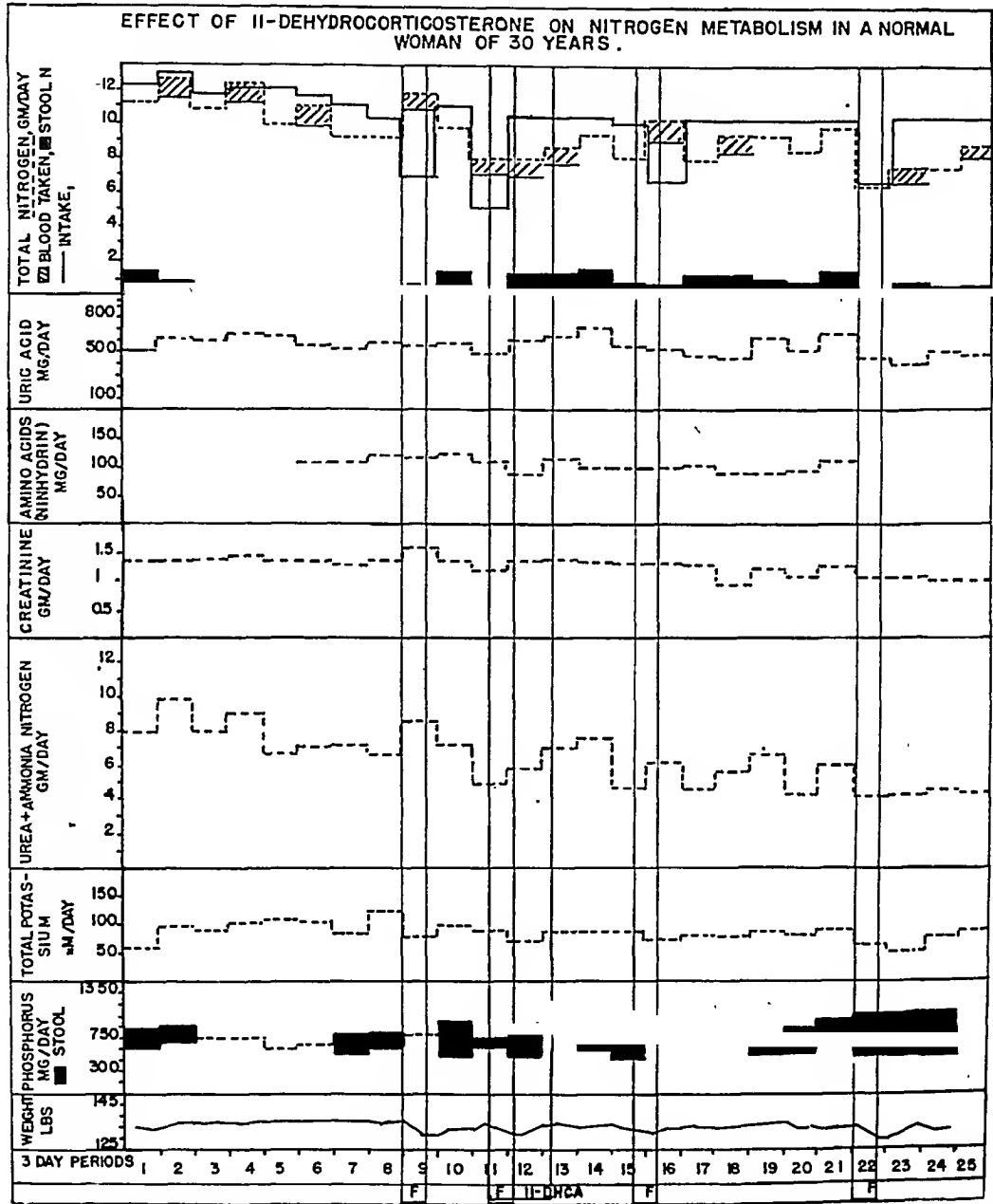


FIG. 1. Nitrogen metabolism, metabolic periods three days. Full lines signify intake, broken lines output. Vertical lines delimit fasting periods (F) and period of medication (11-DHCA). (Intake during fasting periods does not reach zero in chart because metabolic periods are seventy-two hours, fast only forty-eight hours.)

Teleroentgenograms, electrocardiograms and basal metabolic rates were obtained repeatedly before and for a period of ten days after DHCA was given and again following the period of

period and immediately after each fast on alternate days; both were repeated after each fast until they returned to normal before a new fast period was started.

The 11-dehydrocorticosterone acetate (in sesame oil, 100 mg. suspended in 1 ml.) was injected into the gluteus muscle from the thirty-second through the thirty-seventh day of the experiment. Half of the daily dose was given in the morning, the other half seven hours later. The amounts administered were: on the thirty-second day 200 mg., the thirty-third day 400 mg., from the thirty-fourth day through the thirty-seventh day 200 mg. daily. The total amount given was 1,400 mg.

Stools were collected in three-day specimens. Charcoal was used as a marker. Urines were collected daily in twenty-four hour samples. During the fasting periods urines were collected in twelve-hour periods. Acetic acid was used to preserve the urines after the aliquot for 17-ketosteroid determination had been removed; no preservative was used for the stools. All excreta were kept in the refrigerator during collection.

Standard methods described by Peters and Van Slyke⁷ were used for all determinations of chemical blood constituents recorded in Table I and for the determination of all constituents in urine and feces except for those specifically mentioned below. Potassium and sodium in blood, urine and feces were measured by flame photometry;⁸ in the case of the fecal material following dry ashing in a muffle furnace at 500°C. Fecal fat was determined using the wet combustion method.⁷ Amino nitrogen in the blood and urine was measured by the ninhydrin method.⁹ Urinary 17-ketosteroids were measured by the method of Callow¹⁰ and the modification of Talbot.¹¹

Glucose tolerance tests were done as described by Thorn¹² with chemical measurements by the technic of Somogyi, Hartmann and Shaffer.¹³ Insulin sensitivity was measured by determining the blood sugar by the above method every one-half hour for three hours after the intravenous injection of 0.1 unit of insulin per Kg. (U.S.P.). Plasma volume was measured by the use of Evans blue¹⁴ and extracellular water was measured by the use of sodium thiocyanate.¹⁵ The technic employed for the electrophoretic analysis of plasma proteins has been described in detail by Peterman et al.¹⁶

TABLE II
DAILY NITROGEN BALANCE
GM./DAY

Date	Urine	Stool	Total Output	Total Intake	Balance
1946					
May 5-6	6 23				
6-7	8.83	1.26	10.09		
7-8	12 17	1.26	13.43	12 66	- 77
8-9	11.19	1 26	12 45	12.66	*-2 85
9-10	11 70	.75	12 45	12.66	+ .21
10-11	9.00	.75	9.75	12.66	*+2.61
11-12	10.47	.75	11 22	12 66	+1 44
12-13	9 54	1 31	10 85	10 83	- 02
13-14	8.47	1.31	9.78	10.83	+1 05
14-15	9.20	1.31	10.51	12.66	+2.15
15-16	9.76	1.44	11 20	12.66	*-1 69
16-17	10 54	1 44	11.98	10 83	-1.15
17-18	8 81	1.44	10.25	10.83	+ 58
18-19	8 54	1 51	10 05	12.66	+2.61
19-20	7.63	1.51	9.14	10.69	+1 55
20-21	5.46	1 51	6 97	12.66	+5 69
21-22	11 35	1 54	12 89	10 83	-2 06
22-23	8 20	1 54	9 74	12 66	* - 21
23-24	4.01	1.54	5 55	10 80	-5 25
24-25	10 43	1.44	11 87	12 50	+ 63
25-26	7.77	1.44	9 21	10 83	+1 62
26-27	9 32	1.44	10 76	12 66	+1 90
27-28	6 86	.68	7 54	10 83	+3 29
28-29	8 27	.68	8 95	12 66	+3 71
29-30	11.20	.68	11.88	6 90	*-8 13
30-31	7.73	.75	8.45	..	-8 45
31-1	11 25	.75	12.00	7 15	-4 85
June 1-2	9.03	.75	9.78	12 66	+2 88
2-3	7.92	1.37	9 29	10 83	+1.54
3-4	8 12	1.37	9 49	12 61	+3 12
4-5	7.68	1.37	9 05	10.83	+1 78
5-6	6 75	.36	7 11	7 94	+ 83
6-7	5 53	.36	5 89	..	*-7 05
7-8	6 79	.36	7 15	7 15	*-3 60
8-9	6 58	1.05	7 63	10 98	+3 35
9-10	7 46	1 05	8 51	12 80	+4 29
10-11	7 89	1 05	8 94	10 94	+2 00
10-12	7 15	1.07	8 22	12.78	*+1.41
12-13	7.61	1 07	8 68	10 94	+2 26
13-14	4 69	1.07	5 76	12 80	+7 04
14-15	10 53	1 29	11 82	10 98	- .84
15-16	9 30	1 29	10 59	12.80	+2 21
16-17	6 28	1 29	7.57	10.98	+3 41
17-18	8 12	.99	9 11	12 74	+3.63
18-19	6 78	.99	7 77	6.43	-1 34
19-20	6 39	.99	7.38	0	*-9.78
20-21	9.50	.80	10 30	5 85	*-7.00
21-22	8 50	.80	9 30	11.20	+1.90
22-23	7 82	.80	8 62	9 28	+0.66
23-24	6.37	1.04	7.41	11.20	+3.79
24-25	6 48	1.04	7 52	9.28	+1.76
25-26	5 80	1.04	6.84	11 20	+4 36
26-27	9 97	1.11	11 08	9 28	*-2.40
27-28	2 18	1.11	3.29	11.20	*+5.26
28-29	11 09	1 11	12.20	9.28	-2.92
29-30	7.50	.96	8.46	11 20	+2.74
30-1	6 70	.96	7.66	9.28	+1 62

TABLE II (Continued)

Date	Urine	Stool	Total Output	Total Intake	Balance
July 1-2	7.27	.96	8.23	11.20	+2.97
2-3	8.28	.70	8.98	9.28	+0.30
3-4	6.75	.70	7.45	11.20	+3.75
4-5	9.18	.70	9.88	9.28	-0.60
5-6	8.53	1.22	9.75	11.20	+1.45
6-7	7.83	1.22	9.05	9.28	+0.23
7-8	8.85	1.22	10.07	11.20	+1.13
8-9	6.26	.44	6.70	5.70	-1.00
9-10	3.36	.44	3.80	-3.80
10-11	9.04	.44	9.48	5.85	-3.63
11-12	7.30	.79	8.09	11.20	+3.11
12-13	6.70	.79	7.49	9.28	+1.79
13-14	4.60	.79	5.39	11.20	+5.81
14-15	8.32	.56	8.88	9.28	+0.40
15-16	7.74	.56	8.30	11.20	+2.90
16-17	7.58	.56	8.14	9.28	+1.14
17-18	6.90	11.20	

* Nitrogen withdrawn by bleeding included in balance figure.

RESULTS

Throughout the experiment except during periods of fasting the nitrogen balance remained slightly positive. (Fig. 1 and Tables II and III.) No significant effects were noted after the administration of the DHCA. In the more detailed studies of the fasting periods (Fig. 2), it appears that the rise of nitrogen excretion during the end of and following the fasting period was somewhat slower while the compound was administered than it had been in the control fasting periods and before twenty-eight days following DHCA administration. A similar lag of nitrogen excretion behind normal levels was seen in the fasting period five days after the hormone was given. The amino nitrogen excretion during the four fasting periods was essentially unchanged. Blood amino nitrogen fell to a low level at the end of the fast period during which DHCA was given (2.99 mg./100 ml.), whereas the values remained high during the other two fasts after the DHCA injections (4.26 and 4.82 mg./100 ml.). No significant changes in serum phosphorus, proteoses, blood urea and non-protein nitrogen or serum potassium occurred. (Table I.)

Electrophoretic studies of the plasma proteins at various times during the study showed variations which could not be correlated with any known factors and which were within the ex-

TABLE III
URINARY NITROGEN FRACTIONS AND MINERALS EXCRETED
IN 24 HOURS

Date	Urea Nitrogen, Gm/Day	Uric Acid, mg/Day	Creatinine, mg/Day	Amino Nitrogen, mg/Day	Sodium, mM/Day	Potassium, mM/Day	Phosphate, mg/Day
1946							
May 5-6	6.6	271	795		95.2	24.2	557
6-7	9.1	572	1230		102.5	38.2	444
7-8	7.5	690	1968		100.4	106.1	858
8-9	10.6	694	1434		40.6	103.51	671
9-10	10.0	697	1360		22.4	88.5	793
10-11	9.1	602	1421		12.8	83.3	695
11-12	8.7	553	1360		15.04	90.0	787
12-13	7.8	642	1320		88.0	85.5	711
13-14	6.66	578	1380		149.0	90.0	691
14-15	9.40	677	1599		123.0	108.0	728
15-16	8.34	705	1353		84.6	104.0	767
16-17	8.97	693	1414		84.6	83.0	738
17-18	5.77	609	1301		122.0	100.0	528
18-19	6.87	619	1380		87.0	114.8	663
19-20	6.46	492	1260		79.5	85.5	605
20-21	4.81	420	960	76	72.0	81.0	348
21-22	9.04	770	1860	140	96.0	128.3	977
22-23	6.92	624	1360	111	75.0	91.5	635
23-24	3.33	283	680	44	68.0	60.0	239
24-25	10.57	715	1800	123	160.5	92.2	785
25-26	7.50	574	1320	103	126.0	92.2	493
26-27	9.37	657	1560	126	114.0	128.0	781
27-28	5.13	508	1080	100	84.0	90.0	309
28-29	4.74	633	1440	116	132.0	137.0	736
29-30	9.08	816	1980	111	112.5	117.0	1016
30-31	6.05	393	1530	111	50.5	44.3	769
31-1	10.0	492	1300	106	81.5	54.0	1228
June 1-2	6.62	658	1280	118	42.8	90.0	518
2-3	7.87	597	1260	131	129.0	90.0	388
3-4	6.83	522	1560	127	112.5	101.2	593
4-5	5.90	554	1260	115	96.0	101.2	621
5-6	4.64	475	1360	84	62.4	91.5	723
6-7	3.78	385	960	83	33.6	45.6	573
7-8	5.64	583	1390	90	15.6	41.2	629
8-9	5.37	634	1280	110	8.0	64.5	420
9-10	6.68	586	1400	119	30.0	87.0	491
10-11	6.84	625	1240	102	56.0	69.0	518
11-12	7.44	669	1360	115	155.0	90.0	1273
12-13	6.32	649	1586	119	118.95	84.64	620
13-14	5.06	673	920	115*	110.0	67.5	282
14-15	8.29	765	1620	115*	129.0	90.0	797
15-16	7.81	694	1400	115*	161.0	90.0	781
16-17	4.63	514	960	113	119.0	70.5	420
17-18	4.48	623	1440	116	129.0	94.5	434
18-19	4.62	540	1200	111	53.0	60.0	570
19-20	4.63	477	1270	70	60.55	48.4	734
20-21	7.99	557	1320	73	38.4	39.9	719
21-22	6.12	524	1360	105	56.0	78.0	540
22-23	4.48	447	1380	129	75.0	74.2	302
23-24	3.58	408	1160	111	107.0	82.5	471
24-25	5.45	565	1360	94	97.0	67.5	540
25-26	4.81	333	540	110*	71.0	63.8	245
26-27	8.71	803	1720	110*	117.0	85.5	885
27-28	2.16	275	540	110*	40.0	63.75	229
28-29	8.61	716	1480	110*	112.0	90.0	794
29-30	5.95	661	1200	110*	129.0	70.5	508
30-1	4.94	539	1020	110*	129.0	83.25	410
July 1-2	4.71	550	1200	110*	99.0	88.7	583
2-3	5.43	580	1160	110*	99.0	75.0	583
3-4	2.94	400	920	110*	86.0	67.5	470
4-5	6.62	669	1380	110*	109.5	85.5	705
5-6	5.59	604	1200	119	106.0	89.0	622
6-7	5.88	646	1200	104	116.0	84.0	590
7-8	6.47	696	1440	118	136.0	101.0	705
8-9	4.41	430	1080	52	66.0	63.0	515
9-10	2.32	286	816	37	34.4	48.3	296.6
10-11	6.58	503	1130	92	78.0	32.0	595
11-12	5.66	527	1240	113	17.0	64.0	423
12-13	4.41	497	720	90	72.0	66.0	477
13-14	3.56	301	720	66	144.0	65.0	327
14-15	5.44	575	1160	99	124.0	74.0	591
15-16	5.44	586	1240	556	130.0	63.0	508
16-17	5.0	844	1080	622	92.0	77.0	610
17-18	3.97	...	1120	561	116.0	68.0	514

* Represents pooled collections.

perimental errors involved in the determination of plasma volumes and of plasma protein concentration. (Table iv.)

Except for the initial period of salt depletion, three periods were noted (Fig. 3) during which

not parallel variations in humidity or temperature and might be of significance. A trend in the same direction but far less conclusive was noted in the urine excretion of sodium. (Fig. 3, Table III.) While there were no significant changes in

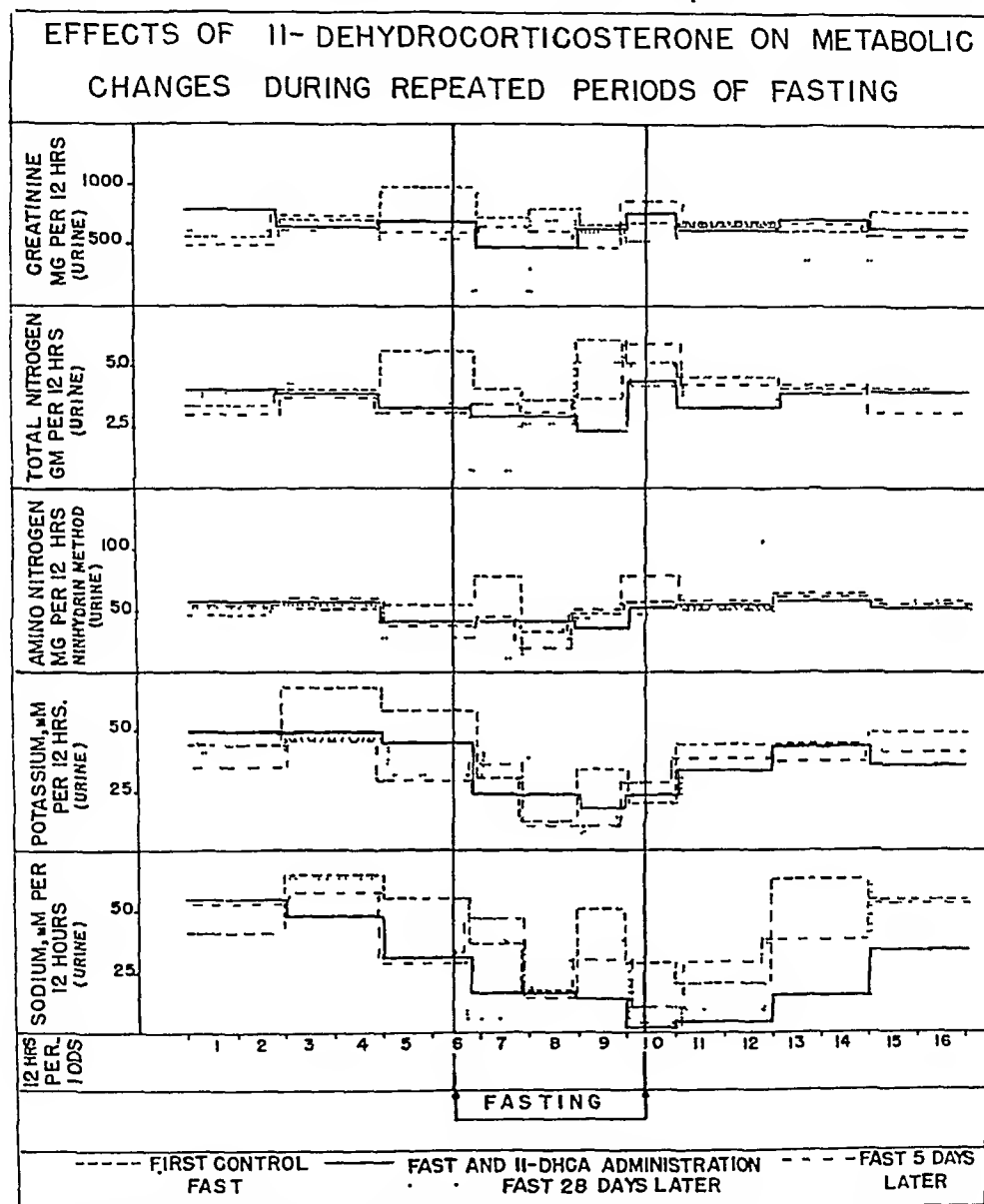


Fig. 2 Nitrogen metabolism during the repeated fasting periods. The four fasting periods are superimposed upon each other on a single time scale

the urine volume gradually decreased (periods 7 to 10, 15 to 18, and 21 to 22). The first and the last of these occurred before menstruation. The one extending from the fifteenth to the eighteenth metabolic period followed the administration of the DHCA. These changes did

the serum concentration of potassium and phosphorus a slight increase of sodium (from 137.8 to 141 meq./l.) occurred sixteen days after the last injection of the DHCA. This coincided with the lowered urinary excretion of this ion.

During the control period three glucose

tolerance curves were obtained which closely corresponded. (Fig. 4, Table v.) This was also true of three insulin sensitivity tests.

After a forty-eight-hour fast without medication the glucose tolerance was decreased. It

after three days (somewhat more rapidly). During this test the blood sugar values, 91 to 117 mg./100 ml., were within the normal range. The insulin sensitivity curves were essentially those obtained during the control period.

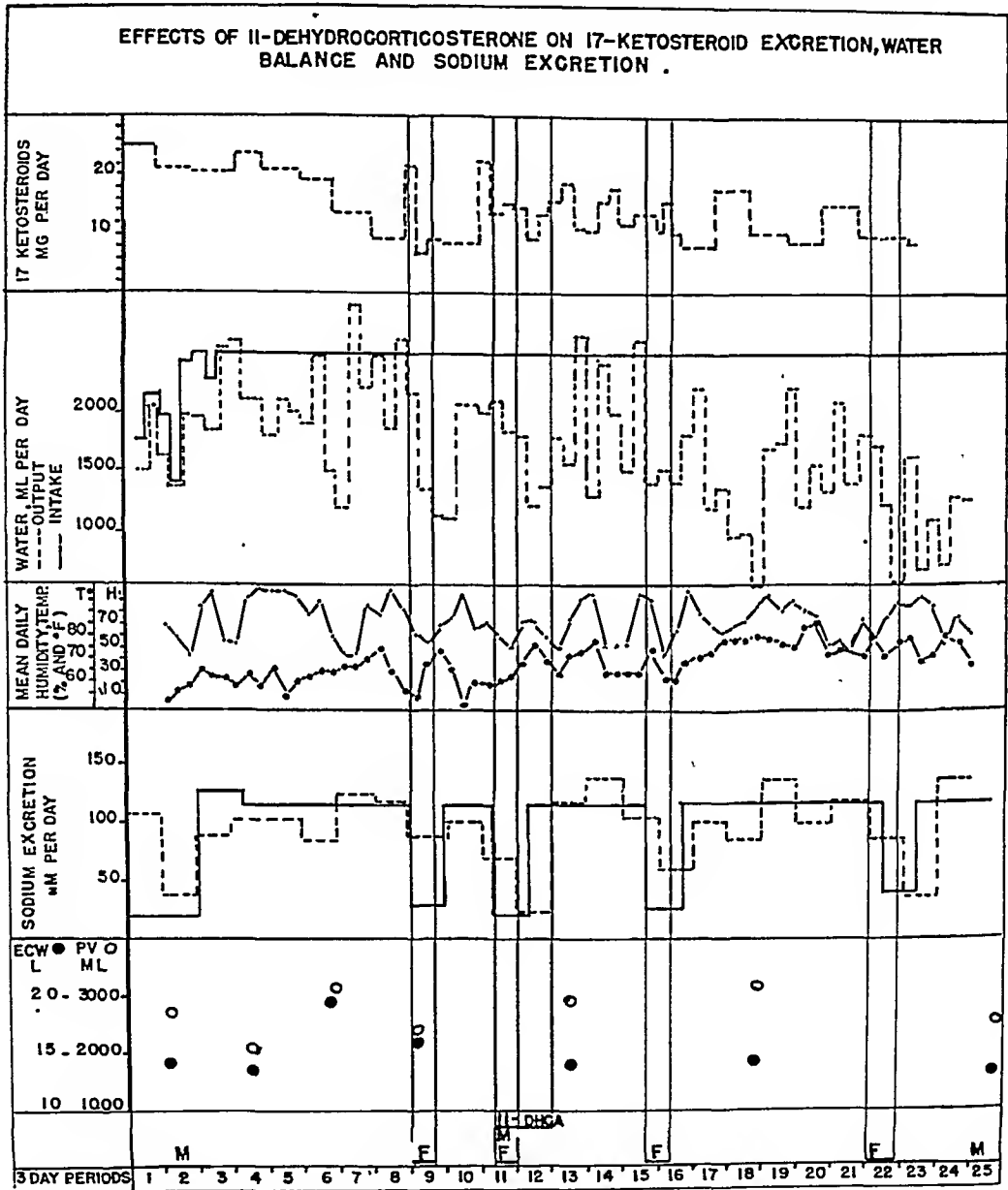


FIG. 3. 17-ketosteroid excretion, fluid balance and sodium balance. Full lines signify intake, broken lines output; metabolic periods three days. Vertical lines delimit fasting periods (F) and period of medication (11-DHCA). M signifies onset of menstruation.

returned to normal within six days after the standard diet had been resumed. Insulin sensitivity was not tested at this point.

After a forty-eight-hour fast during which the hormone was injected, the glucose tolerance was similarly decreased but approached normal

After the third forty-eight-hour fast, ten days following the last injection of 11-dehydrocorticosterone acetate, the glucose tolerance curve was markedly changed. It was flattened with a lower peak. The initial fasting blood sugar was depressed to 80.5 mg./100 ml., and the insulin

sensitivity was decreased (maximal blood sugar fall from 80 to 60 mg./100 ml.). During this fast the blood sugar was low and averaged 77.5 mg./100 ml. Two days later glucose tolerance was decreased, as compared with the normal, and identical with that previously found

TABLE IV
TOTAL CIRCULATING PLASMA PROTEINS

Date	Plasma Volume	Total Protein	Albumin	α_1	α_2	β	ϕ	γ
5-8	2860	187	100	10	17	28	9	22
5-15	2080	140	74	9	14	20	7	16
5-22	3060	192						
5-29	2260	132	64	10	14	22	9	14
6-11	2920	158	81	12	15	25	9	17
6-27	3160	197	101	14	19	33	8	23
7-18	2520	172						

immediately after the forty-eight-hour fasts. This abnormality persisted for eight days after the fast and the insulin sensitivity curves returned to normal nine days after the fasting period.

Twenty-eight days after the last injection of the DHCA the measurements of glucose tolerance and insulin sensitivity were repeated. The slope of the first glucose tolerance curve taken after the fasting was still flat, as it had been after the control fasting period, but the peak of the curve remained within the normal range. Two days later the curve tended to return towards normal and finally became so four days later. Only one fasting blood sugar, obtained six days after the fast, was low (84 mg./100 ml.).

There had been mild reactions to the insulin sensitivity tests in the control period and during the fast when no medication was given; none occurred after the injection of 11-dehydrocorticosterone acetate. One severe "shock-like" reaction occurred during a glucose tolerance test on the fifth day after the fast during hormone administration when the blood sugar level was 70 mg./100 ml.

No ketone bodies were found in the urine during any of the fasts. Glucose was not measured in the urine during the glucose tolerance tests.

TABLE V
FASTING BLOOD SUGAR VALUES

Date	Remarks	Fasting Blood Sugar, mg/100 ml.
5.9	Control Period	98
5.10	124
5.16	114
5.17	118
5.23	112
5.24	114
	Average of Control Period	113.3
	Range	98-124
5.31	After 48 hours fast	107
6.3	113
6.5	114
	Average after fast	111.3
	Range	107-114
6.6 9 AM	During fast—11-DHCA *	91
3 PM	103
9 PM	110.5
6.7 3 AM	117.3
9 AM	105
	Average during fast—11-DHCA	105.4
	Range	91-117
6.10	After fast—11-DHCA	105
6.11	91
6.12	110
6.17	109
	Average after fast—11-DHCA	103.7
	Range	91-109
6.19 9 AM	During fast 10 days after 11-DHCA	80.5
9 PM	80.6
6.20 9 AM	77
1 PM	72
	Average during fast 10 days after 11-DHCA	77.5
	Range	72-80.6
6.21	After fast 12 days after 11-DHCA	82
6.22	91
6.25	149
6.26	96
6.27	117
6.28	89
6.29	117
7.2	103
	Average after fast 12 to 22 days after 11-DHCA	108.8
	Range	82-149
7.8	After last fast 28 days after 11-DHCA	107
7.10	93
7.11	105
7.12	117
7.15	84
7.16	117
7.17	117
	Average after last fast	105.5
	Range	84-117

* 11-DHCA = 11-dehydrocorticosterone acetate.

EFFECTS OF 11-DEHYDROCORTICOSTERONE ON GLUCOSE TOLERANCE AND INSULIN SENSITIVITY TESTS FOLLOWING FASTS

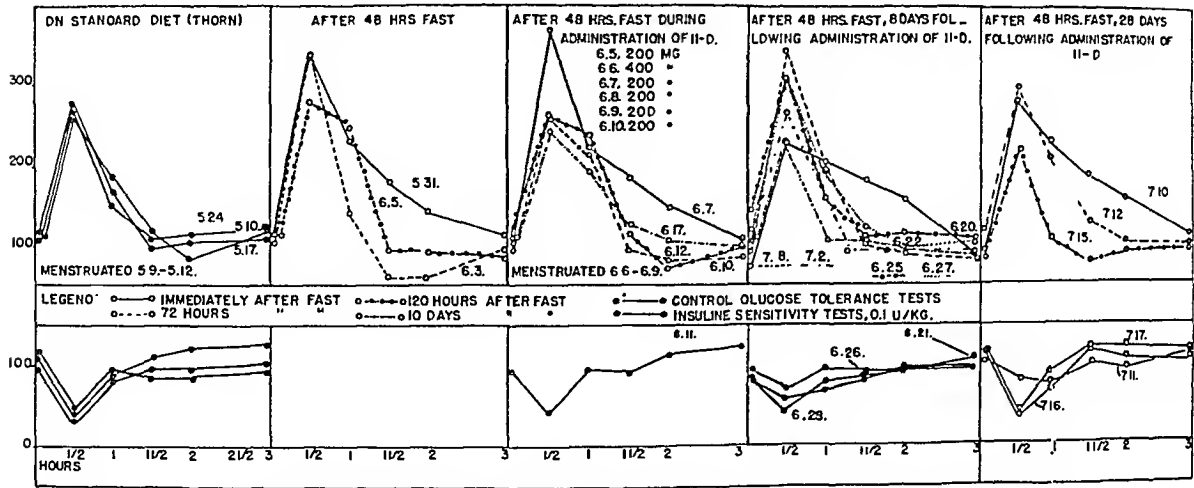


Fig. 4. Carbohydrate metabolism; repeated glucose tolerance and insulin sensitivity tests.

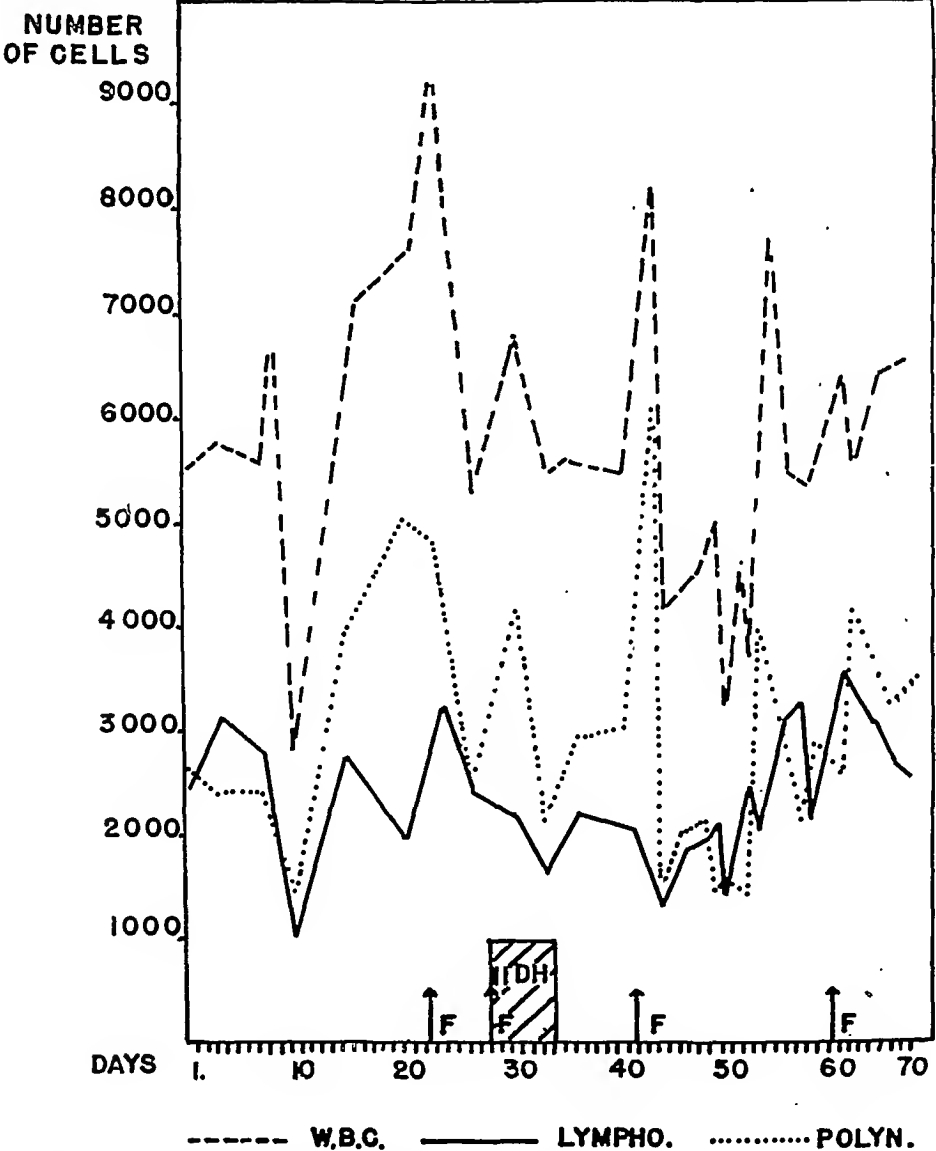


Fig. 5. Leukocytosis in cells/c.mm. showing considerable daily variation and the absence of any consistent change following administration of 11-DHCA.

The fecal excretion of nitrogen diminished by 50 per cent just before the administration of DHCA so that the later return of fecal nitrogen to premedication levels is probably unrelated to DHCA. Phosphorus increased considerably in the feces following the DHCA injection but a similar rise was again seen toward the end of the experiment. The total fat in the feces decreased by 50 per cent during the three days following injection of 11-dehydrocorticosterone acetate to a level of 2.5 Gm./day in the following three day period. Such changes, however, frequently occur in the absence of any medication.

Because of the observations of Dougherty and White¹⁷ and of de la Balze, Reifenstein and Albright¹⁸ blood counts were followed throughout the study. As charted in Figure 5 the variations were considerable but no consistent change followed administration of DHCA.

No significant changes of extracellular water or plasma volume occurred. The basal metabolic rate, electrocardiogram and teleroentgenograms remained normal at all times. A slight and progressive drop of the urinary 17-ketosteroid excretion was not changed by the administration of the hormone. Following the administration of DHCA the patient complained of nausea for two weeks; there were no other subjective changes.

Findings on urinary gonadotropins, results of steroid fractionations and vaginal smears will be reported elsewhere.

COMMENTS

Since the excretion of nitrogen during the periods of fasting with and without administration of 11-dehydrocorticosterone acetate remained essentially the same this compound in the dosage employed apparently exerted no gluconeogenic effects measurable by the methods employed. Likewise, the behavior of the glucose tolerance and insulin sensitivity remained unchanged during the administration of the compound. It seemed at first that ten days after the last injection of DHCA changes in carbohydrate metabolism occurred, blood sugar levels fell and glucose tolerance increased after fasting; however, a few days later

glucose tolerance decreased whereas insulin sensitivity remained impaired. Twenty-eight days after the last injection of the compound the glucose tolerance after fasting was still not exactly that which was obtained after the control fast; hence, these changes could not be definitely ascribed to the DHCA. It does appear possible, nevertheless, that there may be following the administration of an oil suspension of 11-dehydrocorticosterone acetate delayed effects manifested only by the changes in carbohydrate metabolism since all other functions studied remained unchanged or were merely questionably altered.

There was mild sodium retention while the compound was being given, associated with a decreased urine volume. The rise of sodium concentration in the serum coincident with the retention of the ion, however, was insignificant (1.7 per cent).

Possibly, oil suspensions of this compound are absorbed very slowly and studies of their effects may have to be continued far beyond the period of administration of the material. Furthermore, large doses may be needed to produce measurable physiological results. One cannot exclude the possibility that the changes observed were incidental to the repeated periods of fasting, or that they may represent the result of a hormonal imbalance produced by the compound injected rather than direct effects of 11-dehydrocorticosterone acetate itself. Finally, DHCA may have metabolic properties which can be demonstrated readily during anabolism but only with difficulty during fasting.

CONCLUSIONS AND SUMMARY

1. A dosage of 200 to 400 mg. per day of synthetic 11-dehydrocorticosterone acetate (DHCA), a total dose of 1,400 mg., failed to alter the immediate metabolic response to repeated forty-eight-hour fasts in a normal woman.

2. Delayed changes in the response of carbohydrate metabolism to a forty-eight-hour fast ten days after the last injection of DHCA are difficult to interpret and cannot clearly be attributed to 11-dehydrocorticosterone acetate.

3. There was mild retention of sodium and water following the administration of 11-dehydrocorticosterone acetate.

4. The 17-ketosteroid excretion was not increased following injection of 1,400 mg. of 11-dehydrocorticosterone acetate.

The synthetic 11-dehydrocorticosterone acetate used in this study was kindly supplied by Merck and Co., Rahway, N.J. The electrophoresis studies were conducted by Dr. M. L. Petermann, the 17-ketosteroid studies by Dr. K. Dobriner and studies of vaginal smears were made in Dr. E. Shorr's laboratory by Dr. A. C. Carter. The assistance of Dr. E. C. Reifstein, Jr. in the preparation of the manuscript is gratefully acknowledged.

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Effects of Synthetic 11-Dehydrocorticosterone (Compound A) in a Subject with Addison's Disease^{*†}

RANDALL G. SPRAGUE, M.D., CLIFFORD F. GASTINEAU, M.D., HAROLD L. MASON, Ph.D. and
MARSCHELLE H. POWER, Ph.D.

Rochester, Minnesota

THE recent synthesis of 11-dehydrocorticosterone (compound A of Kendall) on a large scale brought with it the hope that this steroid would provide an improved form of treatment for Addison's disease, mainly because the naturally occurring compound had been shown in animal experiments to have effects on the metabolism of both carbohydrate and electrolytes. The only synthetic steroid which has heretofore been generally available for the treatment of Addison's disease, namely, 11-desoxycorticosterone acetate, has profound effects on electrolyte metabolism but is almost totally lacking in carbohydrate activity. Perhaps in part because of this lack, 11-desoxycorticosterone acetate has serious shortcomings in the treatment of chronic adrenal insufficiency. There was reason, therefore, to hope that 11-dehydrocorticosterone might prove to be an important addition to the therapy of this condition.

Reports of the action of synthetic 11-dehydrocorticosterone acetate in cases of adrenal cortical insufficiency in human beings have been made by Forsham, Thorn, Bergner and Emerson and by Perera, Blood and Reinhold. The former investigators studied its effects during short periods in doses varying between 10 and 60 mg. daily

in fourteen patients with Addison's disease; the latter investigators studied its effects in doses varying between 20 and 100 mg. daily in two patients with Addison's disease and in one with adrenal cortical insufficiency secondary to anterior pituitary insufficiency. Both groups of investigators observed that the compound induced retention of sodium chloride and water but that it was relatively deficient in this action as compared to 11-desoxycorticosterone acetate. Forsham, Thorn, Bergner and Emerson reported possible effects of the compound on carbohydrate metabolism in the form of a higher glucose tolerance curve in one patient out of three, a greater fall in serum inorganic phosphorus in two patients out of three during glucose tolerance tests which were done during treatment with 11-dehydrocorticosterone acetate and a consistent effect in preventing symptoms of hypoglycemia in patients with Addison's disease during prolonged fasting and during periods on a low carbohydrate diet. An increased excretion of nitrogen in the urine, 1.2 Gm. per day, was observed in twelve experiments out of fourteen. Perera, Blood and Reinhold, on the other hand, noted no effects on carbohydrate metabolism as measured by fasting respiratory quotients and intravenous glucose tolerance tests. Their patients were

* From the Mayo Clinic, Rochester, Minn.

† The dehydrocorticosterone and dehydrocorticosterone acetate used in this study were kindly supplied by Merck and Company, Inc., Rahway, N. J.

not subjected to the stress of prolonged fasting. However, symptoms of hypoglycemia, at one time associated with a blood sugar level of 57 mg. per 100 cc., were observed in one patient on several occasions when he was receiving 40 mg. of 11-dehydrocorticosterone acetate daily. No definite or consistent effect on nitrogen excretion was observed.

Homburger, Abels, Young and Rhoads observed the effects of 11-dehydrocorticosterone acetate in doses of 200 to 400 mg. per day, totaling 1,400 mg., in a normal young woman. Mild retention of sodium and water followed administration of the hormone but there were no changes in carbohydrate metabolism which could clearly be attributed to the hormone.

Sprague, Kepler, Keating and Power administered naturally occurring 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone to three patients with coexisting Addison's disease and diabetes who consented to act as subjects. The effects of the compounds were measured by means of determinations of the blood sugar and urinary glucose, nitrogen and ketone bodies during fasting after withdrawal of insulin. In only one of the three cases did 11-dehydrocorticosterone in doses of 16 to 50 mg. daily intensify the diabetes appreciably; 17-hydroxy-11-dehydrocorticosterone, on the other hand, in doses of 8 to 20 mg. daily, produced marked intensification of the diabetes in two cases and slight intensification in the third case.

The foregoing studies seem to indicate that 11-dehydrocorticosterone acetate has some effect in inducing retention of salt and water in the human subject but that it is relatively deficient in carbohydrate activity in the doses employed.

The present report deals with a detailed study of the effects of synthetic 11-dehydrocorticosterone in the form of the acetate and the free compound on a patient with

Addison's disease who consented to act as a subject. For purposes of comparison, the effects of 17-hydroxy-11-dehydrocorticosterone* (compound E of Kendall) were also studied.

THE PATIENT

The patient in our study was a woman, aged thirty-eight years, who had Addison's disease of seven years' duration, presumably due to bilateral adrenal cortical tuberculosis. During most of the period since the onset of the disease she had been treated with injections of 11-desoxycorticosterone acetate in a dose of 3 mg. daily. She had a solitary, normally functioning left kidney, the right kidney having been removed in 1935 because of renal tuberculosis. In addition, she had chronic rheumatic mitral endocarditis with stenosis and insufficiency. Except for an episode of congestive heart failure in 1940 induced by overtreatment with 11-desoxycorticosterone acetate, her cardiac function had always been adequate and she had remained in reasonably good health.

METHODS OF STUDY

General. Throughout the study the patient lived in a special metabolic unit of the hospital, designed for the careful measurement of intake and output. She was confined to bed only during glucose and insulin tolerance tests. At other times she was up and about the ward. Her activity was approximately uniform from day to day. She was weighed daily before breakfast. Blood pressure determinations were made four times daily. She remained in good general condition throughout the study and consumed her entire diet daily.

Treatment. In order to prevent interruption of the study by adrenal insufficiency,

*The authors are indebted to Dr. E. C. Kendall for the supplies of 17-hydroxy-11-dehydrocorticosterone used in this study.

a basal treatment of 3 mg. of 11-desoxycorticosterone acetate in sesame oil daily, administered intramuscularly, was employed. To the basal treatment were added, during separate periods of study, 50 mg. of 11-dehydrocorticosterone acetate, 200 mg. of 11-dehydrocorticosterone acetate and 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily administered intramuscularly. In addition, during one period, the basal treatment with 11-desoxycorticosterone acetate was discontinued and the patient received only 100 mg. of free 11-dehydrocorticosterone daily. With the exception of 11-desoxycorticosterone acetate, which was given as a single dose each morning, the daily dose of each steroid employed was injected intramuscularly in two equal parts spaced twelve hours apart.*

* *Procedure for making suspensions of steroids.* The weighed samples of steroids were heated in a covered beaker for one hour at 105°C. Dehydrocorticosterone and its acetate were ground to a fine powder in a sterile agate mortar. A portion of the required amount of autoclaved sesame oil was added and grinding was continued until most of the steroid was in suspension. The suspension was transferred with a sterile pipet to a sterile rubber-capped bottle. The mortar was rinsed with successive portions of sesame oil until all of the steroid and all of the required amount of sesame oil had been transferred to the bottle. The pipet was rinsed with 0.5 cc. of acetone which was added to the suspension. A cotton plug was placed in the mouth of the bottle and it was heated one hour in an oven at 105°C. The rubber cap was then put in place and the bottle was shaken until cold to avoid formation of large crystals by the steroid which crystallized out of the oil on cooling. Sesame oil containing 2 per cent of benzyl alcohol was also used but the benzyl alcohol did not increase the solubility of the steroids sufficiently to be of any advantage.

The weighed sample of 17-hydroxy-11-dehydrocorticosterone was dissolved in alcohol, the required amount of sesame oil was added and the alcohol was removed in a vacuum. As soon as the oil became cloudy from separation of the steroid it was transferred to a bottle and heated at 105°C. for two hours. The bottle was capped and shaken until cold.

The concentrations of the various steroids in sesame oil were as follows: 11-dehydrocorticosterone acetate (dose, 50 mg. daily), 25 mg. per cc.; 11-dehydrocorticosterone acetate (dose, 200 mg. daily), 100 mg. per cc.; 11-dehydrocorticosterone (dose, 100 mg. daily), 50 mg. per cc.; 17-hydroxy-11-dehydrocorticosterone (dose, 20 mg. daily), 10 mg. per cc.

A commercial preparation of 11-desoxycorticosterone acetate in sesame oil, containing 5 mg. per cc., was employed.

The usual period of administration of a given steroid was eight or nine days. Urine collections were made each twenty-four hours for the first six days; on the seventh day a glucose tolerance test was performed and on the eighth day an insulin tolerance test. In some instances, the patient was made to fast on the ninth day.

Diet. The diet was weighed. Three menus were employed, each menu twice in each six-day period. The daily intake of carbohydrate averaged 219 Gm., of protein, 61 Gm. and of fat, 68 Gm. The diet was supplemented with 7 Gm. of sodium chloride and 1 Gm. of potassium (in the form of potassium citrate) daily. Figures for the composition of the diet, obtained by direct analysis and addition of the supplements of sodium chloride and potassium in the case of electrolytes and nitrogen, and from standard tables in the case of carbohydrate, protein and fat, are given in Table 1. Water intake (as drinking water) was 1,500 cc. daily.

Studies of Electrolyte Metabolism. Urinary excretion of sodium, potassium, chloride and phosphorus was measured daily during periods of six days each. Plasma sodium, potassium, chloride, carbon dioxide content and urea and hematocrit were determined on venous blood on the first day of each period.

Studies of Carbohydrate Metabolism. Determinations of the fasting blood sugar were made every other morning. Glucose tolerance tests were performed on the seventh day of most periods by administering 0.5 Gm. of glucose per Kg. of ideal body weight in a 20 per cent solution intravenously during a period of thirty minutes. Insulin tolerance tests were performed on the eighth day of most periods by administering 0.05 unit of insulin per Kg. of ideal body weight intravenously, a solution of insulin containing 5 units per cc. being employed. The blood sugar was determined at intervals

during several periods of fasting of twenty-four hours each. All determinations of blood sugar were made on capillary blood. Total urinary nitrogen was estimated daily.

Miscellaneous Studies. Periodic determinations of urinary 17-ketosteroids and "cortin-

son, respectively, and lecithin by the method of Youngburg and Youngburg.

Urinary 17-ketosteroids were determined by the technic of Callow and associates,^{5,6} employing a correction equation to compensate for the overestimation due to

TABLE I
DAILY INTAKE DATA

Menu	Total, Gm.				Calories	Total, mEq.		
	Carbohydrate	Protein	Fat	Nitrogen		Sodium	Potassium	Chloride
1	220	63	65	10.21	1,717	154	92	173
2	222	60	63	9.52	1,695	168	104	182
3	216	60	75	10.45	1,779	148	98	172
Average	219	61	68	10.06	1,732	157	98	176

like" substances were made. Blood cholesterol, cholesterol esters, lecithin, fatty acids and total lipoids, and total serum protein and albumin-globulin ratio were determined at intervals.

Chemical Methods. Blood sugar was determined by the procedure described recently by Somogyi; albumin and total protein in serum by a modification of the biuret procedure of Kingsley; chlorides in plasma by a modification of the method of Keys, and in urine by a modified Volhard-Harvey titration; sodium in plasma and urine by the method of Butler and Tuthill; potassium in plasma and urine by Hartzler's modification of the chloroplatinate method of Shohl and Bennett; inorganic phosphorus in plasma and urine by the method of Gomori; carbon dioxide content¹⁴ and urea¹⁵ of plasma according to the manometric procedures described by Peters and Van Slyke; urinary total nitrogen by the Kjeldahl method; total lipid fatty acids plus cholesterol in plasma by the method of Bloor; cholesterol and cholesterol esters by the methods of Bloor, and Bloor and Knud-

son, respectively, and lecithin by the method of Youngburg and Youngburg.

RESULTS

Studies of Electrolyte Metabolism. There was little change in the electrolyte pattern of the plasma during the several programs of treatment. (Table II.)

The principal effect of 11-dehydrocorticosterone on electrolyte and water balance was a decrease in the excretion of sodium chloride and water for several days (during period 5) following the administration of 200 mg. of the acetate daily for eight days. (Fig. 1, Table III.) At the same time there was a decrease in the excretion of potassium in the urine. During the few days that sodium chloride and water were being retained there was a gain of 2 Kg. of body weight associated with the development of edema and there was a slight rise in mean blood pressure and an increase in cardiac size. These effects occurred after administration of the compound had been stopped

TABLE II
HEMATOCRIT, BLOOD SUGAR, PLASMA UREA AND PLASMA ELECTROLYTE VALUES
DURING VARIOUS PROGRAMS OF TREATMENT

Period	Daily Treatment*	Days†	Mg. per 100 cc.		Hematocrit, Per Cent Cells	mEq. per Liter			
			Sugar‡	Urea		CO ₂	Chloride	Sodium	Potassium
1	3 mg. DOCA	8	73 (70-83)	30	33	26	106	137	4.9
2	50 mg. DHCA + 3 mg. DOCA	8	81 (71-86)	29	33	25	106	137	4.6
3	3 mg. DOCA	8	76 (73-83)	24	32	27	106	137	4.4
4	200 mg. DHCA + 3 mg. DOCA	8	80 (76-83)	24	31	..	104	135	3.7
5	3 mg. DOCA	14	81 (79-86)	25	30	..	107	139	4.0
6	3 mg. DOCA	6	81 (76-86)	25	34	26	104	134	4.2
7	3 mg. DOCA	6	76 (53-86)	23	35	..	104	133	3.6
8	20 mg. 17-OH-11-DHC + 3 mg. DOCA	9	77 (64-100)	23	33	..	105	134	4.1
9	3 mg. DOCA	12	79 (70-86)	25	34	..	106	136	4.0
10	100 mg. DHC	11	86 (83-89)	24	32	..	107		

* DOCA = 11-desoxycorticosterone acetate; DHCA = 11-dehydrocorticosterone acetate; 17-OH-11-DHC = 17-hydroxy-11-dehydrocorticosterone; DHC = 11-dehydrocorticosterone.

† Refers to the number of days the various steroids were administered before analyses of the blood for electrolytes were performed.

‡ Upper figure is average; figures in parentheses are minima and maxima.

TABLE III
URINARY EXCRETION OF ELECTROLYTES AND NITROGEN DURING VARIOUS
PROGRAMS OF TREATMENT*

Period	Treatment	Days†	Average Excretion, mEq. per 24 Hours			Total Nitrogen, Gm. per 24 Hours
			Chloride	Sodium	Potassium	
1	3 mg. DOCA	5‡	149	149	83	7.15
2	50 mg. DHCA + 3 mg. DOCA	6	139	132	85	7.26
3	3 mg. DOCA	6	143	135	90	8.18
4	200 mg. DHCA + 3 mg. DOCA	6	153	147	88	8.02
5	3 mg. DOCA	6	122	130	71	7.99
6	3 mg. DOCA	6	173	177	85	8.60
7	3 mg. DOCA	6	167	167	89	8.45
8	20 mg. 17-OH-11-DHC + 3 mg. DOCA	6	141	148	86	8.70
9	3 mg. DOCA	6	147	146	92	8.36
10	100 mg. DHC	6	142	133	81	8.06

* The same data are charted in Figure 1.

† Refers to number of days of urine collection, not to number of days of administration of the various steroids.

‡ Specimen for one day of the six-day collection period was lost.

and could reasonably be attributed to a delayed action of the compound owing to its low solubility in the tissue fluids.* Coinciding with these changes there was an increase in "cortin-like" compounds in the

but was followed by retention of sodium and chloride despite continued administration of the compound, so that the average daily excretion for the period was approximately the same as during control periods.

TABLE IV
URINARY EXCRETION OF 17-KETOSTEROIDS AND "CORTIN-LIKE" COMPOUNDS DURING VARIOUS PROGRAMS OF TREATMENT

Daily Treatment	17-Ketosteroids		"Cortin-like" Compounds	
	Determinations	Average Excretion, Mg. per 24 Hours	Determinations	Average Excretion, Mg. per 24 Hours*
3 mg. DOCA	3	0.7	4	0.051
50 mg. DHCA + 3 mg. DOCA	1	0.3	7	0.091
3 mg. DOCA	2	1.1	5	0.060
200 mg. DHCA + 3 mg. DOCA	2	0.8	8	0.172
3 mg. DOCA	2	0.303†
3 mg. DOCA	3	1.1	5	0.077
20 mg. 17-OH-11-DHC + 3 mg. DOCA	2	0.8	3	0.234
3 mg. DOCA	4	0.084
100 mg. DHC	11	0.245

* The quantity of "cortin-like" compounds is expressed in terms of mg. of 11-dehydrocorticosterone.

† Determinations made on the two days immediately following cessation of treatment with 200 mg. of 11-dehydrocorticosterone acetate daily.

urine. (Table iv.) These effects gradually reversed themselves during the succeeding two periods.

During and after the period of administration of 50 mg. of 11-dehydrocorticosterone acetate daily (period 2), there was a slight decrease in excretion of sodium chloride, of questionable significance. During the period of administration of 100 mg. of free 11-dehydrocorticosterone daily (period 10) there was a progressive decrease in excretion of sodium chloride associated with a gain of body weight. (Fig. 1.)

During the first two days of administration of 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily, the excretion of sodium and chloride in the urine increased. However, this increase not only failed to persist

* It is to be noted that these changes were first observed three days before a menstrual period, that is, at a time when menstrual edema might be expected to occur. However, this explanation for the retention of salt and development of edema seemed to be ruled out by the fact that the patient never before or subsequently had frank edema preceding menstruation.

Studies of Carbohydrate Metabolism. Changes in the level of the fasting blood sugar during the various programs of treatment were of small magnitude and probably not significant. (Table II.) Variations in urinary nitrogen were of small magnitude. (Fig. 1.)

Likewise, there was little or no alteration in the blood sugar curves during glucose tolerance tests. (Fig. 2.)

Insulin tolerance tests showed a smaller maximal depression of the blood sugar level and a higher blood sugar level at the conclusion of the test when the patient was receiving 200 mg. of 11-dehydrocorticosterone acetate or 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily than when she was receiving the basal treatment alone. (Fig. 3.) In view of the limited amount of data, the changes are probably not of sufficient magnitude to be clearly attributed to the compounds in question but they are suggestive of an effect on carbohydrate

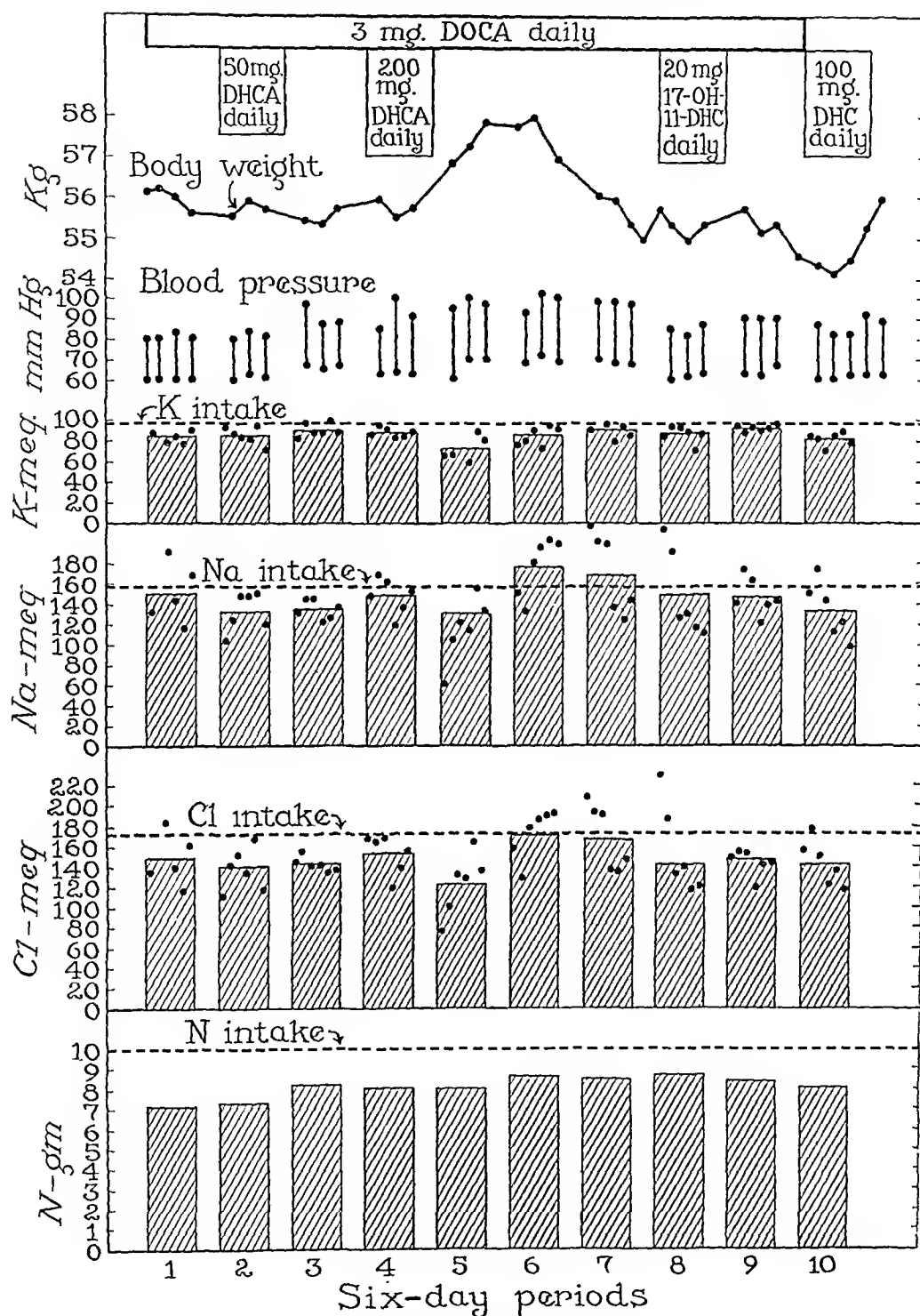


FIG. 1. Data relative to treatment, body weight, blood pressure and urinary excretion of potassium, sodium, chloride and nitrogen in a patient with Addison's disease. DOCA is 11-desoxycorticosterone acetate; DHCA, 11-dehydrocorticosterone acetate; 17-OH-11-DHC, 17-hydroxy-11-dehydrocorticosterone; DHC, 11-dehydrocorticosterone. Cross-hatched columns represent average daily excretion; dots represent daily excretion.

metabolism. The changes were most marked in the case of 17-hydroxy-11-dehydrocorticosterone.

Hypoglycemia occurring in the course of insulin tolerance tests seemed to be better tolerated (subjectively) when the patient

sterone daily than when she was receiving 11-desoxycorticosterone acetate alone. (Fig. 4.) While the differences in decline of the blood sugar during the several fasts were not great, they were of sufficient magnitude to be suggestive of some carbohydrate

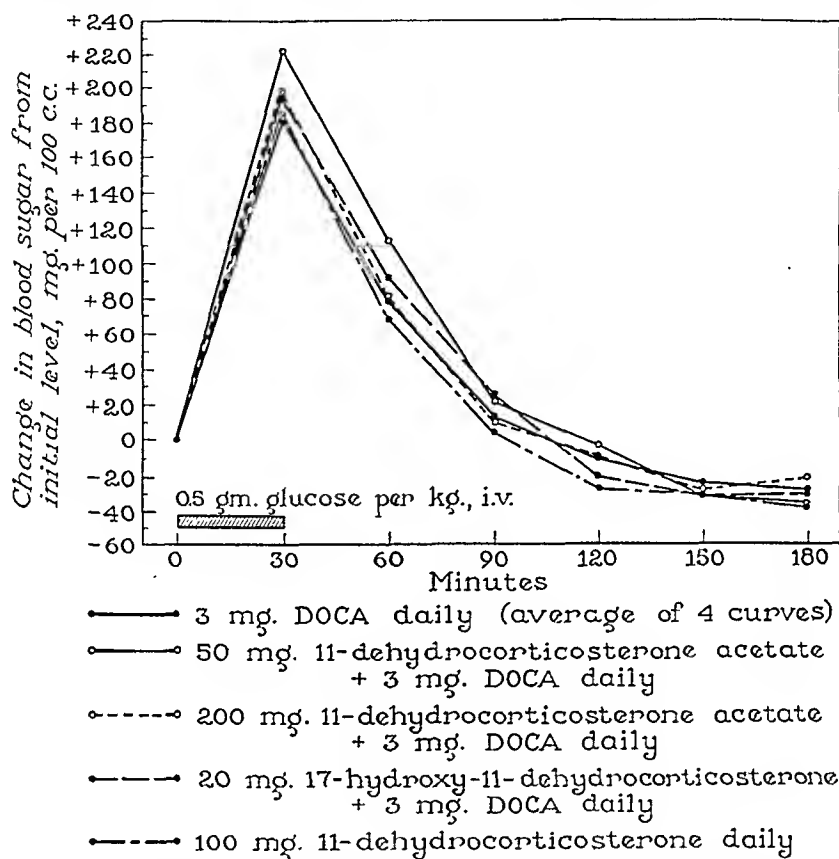


FIG. 2. Glucose tolerance curves in a patient with Addison's disease during various programs of treatment. The points of each curve are charted as change in blood sugar from starting level, in milligrams per 100 cc.

was receiving either 11-dehydrocorticosterone, 11-dehydrocorticosterone acetate or 17-hydroxy-11-dehydrocorticosterone than when the basal treatment with 11-desoxycorticosterone acetate alone was employed. The subjective improvement, while not susceptible of measurement, seemed to be most marked when she was receiving 17-hydroxy-11-dehydrocorticosterone.

During the course of a fast of twenty-four hours there was less fall of the blood sugar while the patient was receiving either 100 mg. of 11-dehydrocorticosterone, 200 mg. of 11-dehydrocorticosterone acetate or 20 mg. of 17-hydroxy-11-dehydrocortico-

activity on the part of free 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone, particularly the latter compound.

Other Studies. The administration of 11-dehydrocorticosterone and of 17-hydroxy-11-dehydrocorticosterone resulted in moderate increases of "cortin-like" compounds in the urine. (Table iv.) No significant change in the urinary excretion of 17-ketosteroids was noted.

No consistent effects of the various programs of treatment on blood lipoids, serum proteins, albumin-globulin ratio or urinary phosphorus were observed.

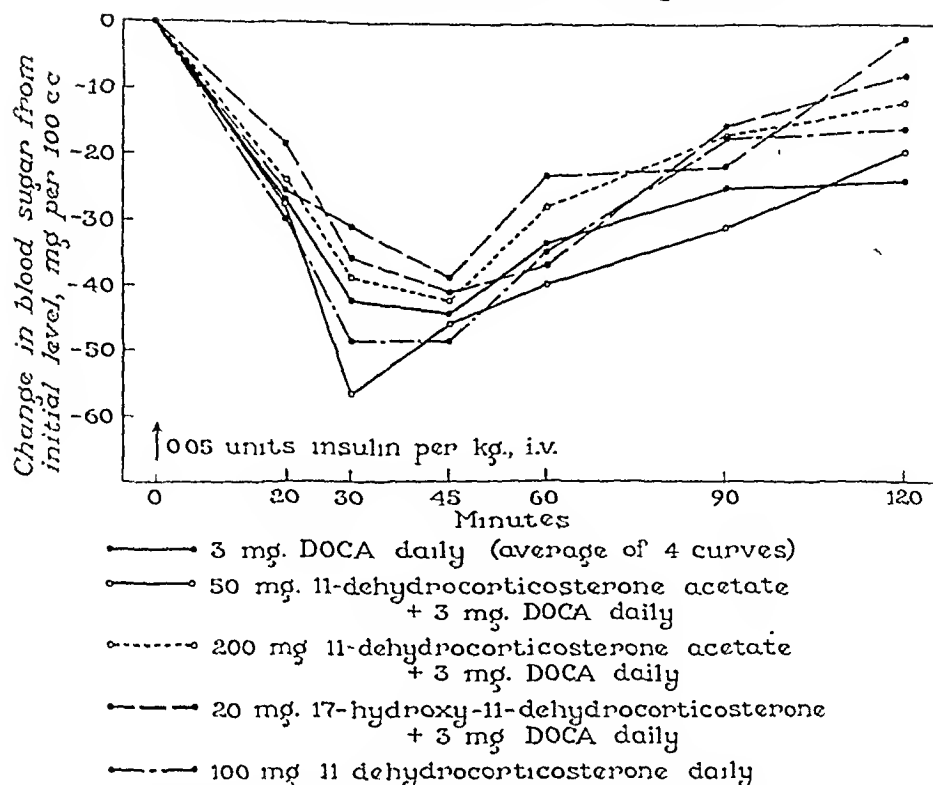


FIG. 3. Insulin tolerance curves in a patient with Addison's disease during various programs of treatment. The points of each curve are charted as change in blood sugar from starting level, in milligrams per 100 cc.

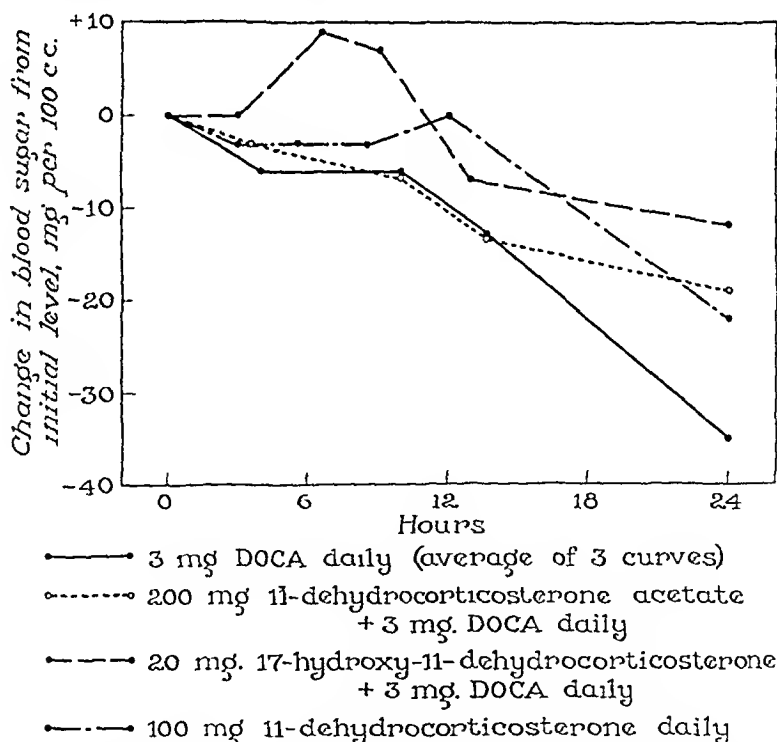


FIG. 4. Changes in level of blood sugar in a patient with Addison's disease during twenty-four hour fast on various programs of treatment. In each instance the period of fasting was considered as beginning in the morning at 0 hour which was fourteen hours after the last meal.

COMMENT

Studies on animals have clearly demonstrated that 11-dehydrocorticosterone is capable of influencing the metabolism of carbohydrate and electrolytes. The present study, and also other recent studies, indicate that it is not a simple matter to demonstrate these activities in the human subject.

The observations which we have recorded indicate that the compound in doses up to 200 mg. of the acetate daily has a slight influence on electrolyte metabolism as indicated by retention of sodium chloride and water. The data disclose no more than a hint of carbohydrate activity in the form of minor alterations of the insulin tolerance curve and the blood sugar during fasting. It seems probable that the carbohydrate and electrolyte effects which have been clearly demonstrated in animals could be duplicated in the human subject if it were possible to expose the tissues to a higher concentration of the steroid. Unfortunately, the low solubility of the compound limits the amount which can be conveniently introduced into any given subject by parenteral injection.

As already noted, this patient had only one kidney. Forsham, Thorn, Bergner and Emerson suggested that the total mass of functioning renal tissue might be a limiting factor in the response to the compound, as measured by its effects on nitrogen and electrolyte excretion. This seems to be a reasonable suggestion and may account, in part at least, for the minimal "renal response" of our patient to the compound. However, even taking into account the possible functional limitations of a solitary kidney, it is difficult to escape the conclusion that 11-dehydrocorticosterone in the doses employed was, by comparison with 11-desoxycorticosterone acetate, relatively deficient in electrolyte activity.

In this patient 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily did not produce as striking changes in carbo-

hydrate metabolism as have been observed in patients with coexisting Addison's disease and diabetes in response to even smaller doses. Nevertheless, the observations made on this latter group of patients as well as data from numerous experiments on animals, leave no room for doubt that the carbohydrate activity of 17-hydroxy-11-dehydrocorticosterone is much greater than that of 11-dehydrocorticosterone.

In the present study it was noted that 17-hydroxy-11-dehydrocorticosterone induced only a transient increase in sodium excretion, which did not persist with continued administration of the compound. This observation suggests that the increase in sodium and chloride excretion which has been observed after only a single injection of this compound¹⁹ may not provide an adequate basis for a description of its electrolyte activity.

It appears, on the basis of this study, as well as others, that 11-dehydrocorticosterone will have a very limited clinical usefulness, if any, in the treatment of Addison's disease, unless it should prove feasible to administer relatively tremendous doses, perhaps by mouth, at reasonable cost to the patient. Nevertheless, the physiologic effects and metabolism of this steroid, as well as other pure steroids of adrenal origin, deserve further study in human subjects. It is therefore to be hoped that the shortcomings of 11-dehydrocorticosterone as a therapeutic tool will not result in its becoming unavailable for further experimental study.

SUMMARY AND CONCLUSIONS

1. A study of the effects of synthetic 11-dehydrocorticosterone (both the acetate and the free compound) on a patient with Addison's disease was carried out. Doses from 50 to 200 mg. daily were employed. The effects of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily were also studied.

2. After a period of administration of

11-dehydrocorticosterone acetate in a dose of 200 mg. daily there was a decrease in the urinary excretion of sodium chloride and water, a gain of body weight due to edema, a slight rise in blood pressure and an increase in cardiac size. There was also a decrease in urinary excretion of salt and water during a period of administration of 100 mg. of free 11-dehydrocorticosterone daily.

3. Effects of 11-dehydrocorticosterone on carbohydrate metabolism, studied by means of determinations of the fasting blood sugar, glucose and insulin tolerance tests, changes in the blood sugar during prolonged fasting and estimations of urinary nitrogen, were slight and in most instances of questionable significance.

4. The administration of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily resulted in a transient increase in the urinary excretion of sodium chloride. The compound in this dose had slight carbohydrate effects, as indicated by a diminished hypoglycemic response to insulin and better maintenance of the blood sugar level during fasting.

5. Both 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone produced increases in the urinary excretion of "cortin-like" substances in the urine. Neither produced any change in the urinary excretion of 17-ketosteroids.

6. Neither compound produced consistent changes in blood lipoids, serum proteins, albumin-globulin ratio or urinary phosphorus.

The authors are indebted to Miss Lida Burrill, chief dietitian, Mayo Clinic metabolic unit, St. Marys Hospital, for her careful planning and supervision of the diets used in this study.

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Sodium Loss in Man Induced by Desoxycorticosterone Acetate*

Study in a Subject with Myotonic Dystrophy

K. L. ZIERLER, M.D. and J. L. LILIENTHAL, JR., M.D.

with the technical assistance of

MARJORIE GLASS and MARTHA JAFFE

Baltimore, Maryland

DESOXYCORTICOSTERONE acetate (DCA) administered in large doses to normal dogs causes polydipsia and polyuria which then disappear within about one week of withdrawal of the steroid.^{7,12} These results do not appear in normal cats to whom DCA is exhibited.¹⁹ Normal man, given smaller doses for a time shorter than necessary to produce polydipsia and polyuria in dogs, responds to DCA by retaining sodium and water.¹⁵

The purpose of this paper is to report the production by DCA of a syndrome, reminiscent of that which occurs in dogs, in a patient with myotonic dystrophy. In an effort to understand the mechanism of this syndrome, we have measured the effects of DCA on the overall nitrogen, sodium and potassium metabolism and on certain renal glomerular and tubular processes.

PLAN OF STUDY AND METHODS

The subject, B. R., Unit No. 393446, was a fifty-eight year old white male with myotonic dystrophy. In addition to profound muscle atrophy and myotonia, the patient had a non-toxic nodular goiter, bilateral testicular atrophy and gynecomastia. Daily excretion of the follicle-stimulating hormone was not elevated.† With the exception of a depressed excretion of 17-ketosteroids‡ (2

† These measurements were kindly done by Drs. Lawson Wilkins and Roger A. Lewis, Department of Pediatrics.

* From the Physiological Division, Department of Medicine, The Johns Hopkins University and Hospital, Baltimore, Md. The work was done under a contract between the Office of Naval Research, U. S. Navy Department and the Johns Hopkins University.

mg. per day), there were no stigmata of corticoadrenal disease prior to DCA administration. Serum concentrations of sodium (144 mEq./L.) and of potassium (4 mEq./L) were normal and the patient responded to sodium restriction (27 mEq. of sodium daily for ten days) by retaining sodium in a fashion compatible with normal corticoadrenal function.

DCA in oil** was administered intramuscularly in doses of 5 to 15 mg. daily for seventeen days and, after an interval of seventy days, 10 mg. daily for ten days.

The patient was maintained on a constant diet calculated to contain 50.4 Gm. of protein, 149.4 Gm. of carbohydrate, 60.7 Gm. of fat and 1,345 calories. Sodium intake was regulated by supplementing a sodium-poor diet with enteric-coated¹ sodium chloride tablets. The diet was analyzed periodically for nitrogen by a macro-Kjeldahl method¹ and for sodium and potassium by the flame photometer.⁵ Stools for each period were pooled and analyzed for nitrogen, sodium and potassium. Urine was collected daily and preserved with 10 ml. of 25 per cent acetic acid. The excretion of nitrogen, sodium, potassium and, during the latter half of the study, chloride (by the method of Harvey⁶) was measured. Serum sodium and potassium concentrations and the concentrations of glucose and of non-protein

** Percorten, generously supplied by Ciba Pharmaceutical Products, Inc.

nitrogen in the blood were determined at intervals.

Water intake was unrestricted. The difference between water intake and urine volume was assumed to be a function of fluid balance. Body weight was recorded daily.

Creatine was measured by the method of Peters.¹¹

RESULTS

The overall balances of nitrogen, electrolytes and water appear in Table 1 and Figure 1.

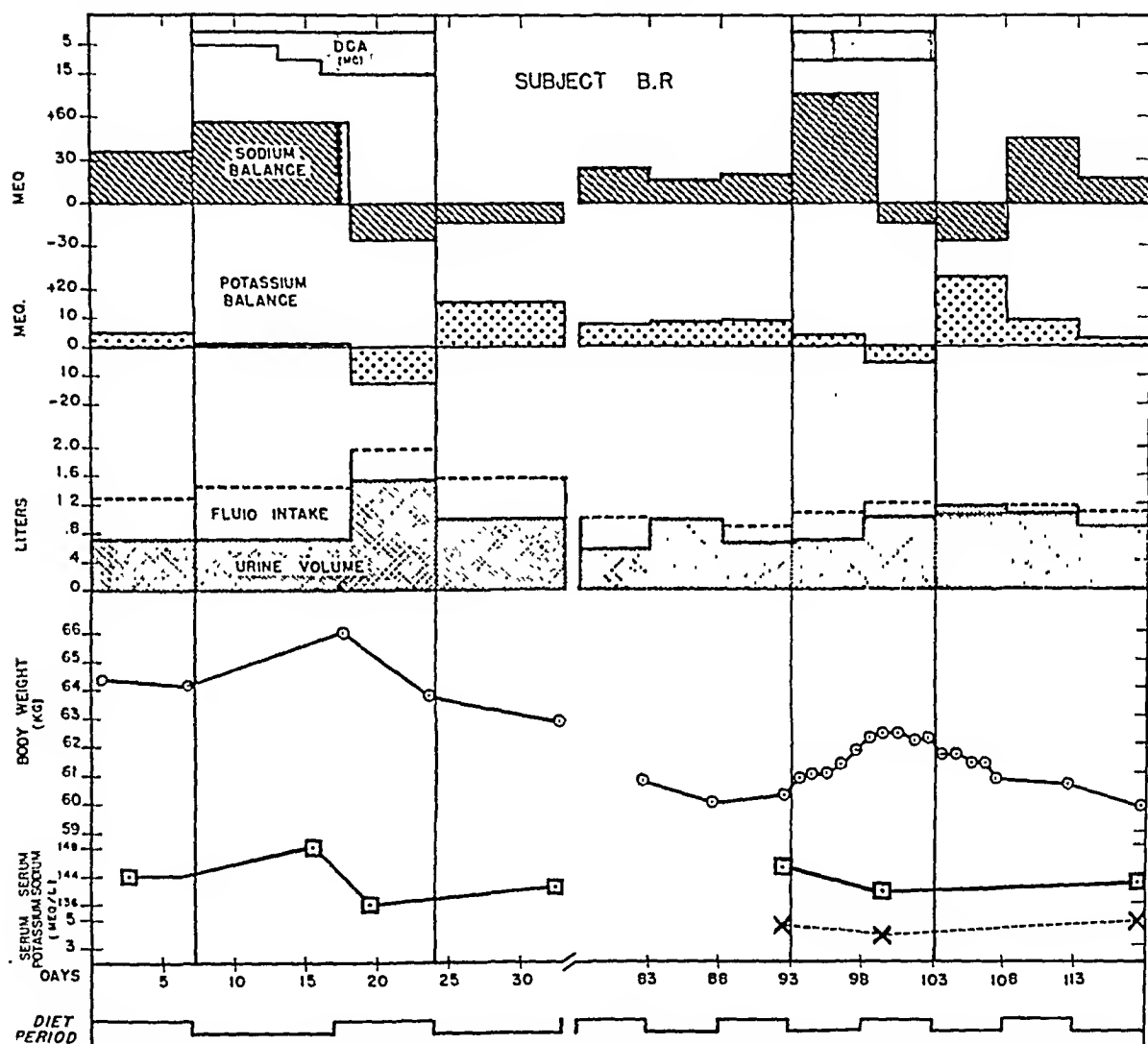


FIG. 1. Effect of DCA on sodium and on potassium balance, on fluid intake, urine volume, body weight and concentrations of sodium and of potassium in serum. Balances, fluid intakes and urine volume are charted as averages for each diet period. (See Table 1 for daily data.)

The simultaneous renal clearances of mannitol, by the single injection technique of Newman et al.,¹⁰ and of creatine were measured prior to the first course of DCA and repeated on the last day of the first course. Creatine clearance was measured during rising serum concentrations following the ingestion of 25 Gm. of creatine hydrate.

Observations during the second period of study were similar to those of the first. The initial effects of DCA were retention of sodium and of chloride, less positive potassium balance, unaltered nitrogen balance, water retention with a corresponding increase in body weight and the appearance of mild edema of the face.

TABLE I
METABOLIC DATA FROM EXPERIMENTS I AND II IN SUBJECT B. R.

Day	Fluid Intake (ML.)	Urine Volume (ML.)	Sodium (mEq.)			Potassium (mEq.)			Chloride (mEq.) Urine	Nitrogen (Gm.)			DCA* (Mg.)
			Diet	Urine	Fecal	Diet	Urine	Fecal		Diet	Urine	Fecal	
1	950	158	116	8	56	40	14	...	8.9	5.2	1.1	
2	590	1100	158	163	8	56	52	14	...	8.9	8.3	1.1	
3	1370	650	158	88	8	56	..	14	...	8.9	6.8	1.1	
4	1420	600	158	83	8	56	39	14	...	8.9	6.6	1.1	
5	1830	750	158	97	8	56	34	14	...	17.9	8.7	1.1	
6	158	...	8	56	..	14	...	8.9	1.1	
7	1570	800	158	136	8	56	35	14	...	8.9	8.1	1.1	
8	1270	600	160	63	7	55	48	12	...	8.3	6.6	1.1	5
9	1370	600	160	70	7	55	48	12	...	8.3	6.8	1.1	5
10	1700	600	160	74	7	55	35	12	...	8.3	5.3	1.1	5
11	1795	750	160	101	7	55	..	12	...	8.3	6.8	1.1	5
12	1820	650	160	84	7	55	41	12	...	8.3	5.8	1.1	5
13	1445	1300	160	176	7	55	46	12	...	8.3	6.9	1.1	5
14	1120	700	160	85	7	55	40	12	...	8.3	6.1	1.1	10
15	1370	1100	160	153	7	55	49	12	...	8.3	6.8	1.1	10
16	1470	840	160	100	7	55	..	12	...	17.3	9.0	1.1	10
17	160	77	7	55	23	12	...	8.3	3.6	1.1	15
18	2120	600	193	81	7	43	31	14	...	8.4	5.3	0.9	15
19	1520	1150	193	175	7	43	41	14	...	8.4	6.5	0.9	15
20	2070	1850	193	221	7	43	43	14	...	8.4	5.6	0.9	15
21	1920	1520	193	210	7	43	43	14	...	8.4	6.5	0.9	15
22	1995	1870	193	167	7	43	45	14	...	8.4	6.0	0.9	15
23	1770	1370	193	188	7	43	39	14	...	14.7	8.4	0.9	15
24	193	...	7	43	..	14	...	8.4	...	0.9	15
25	1330	650	161	81	7	48	10	9	...	8.0	5.0	1.0	
26	1770	1100	161	152	7	48	11	9	...	8.0	5.2	1.0	
27	2070	1170	161	185	7	48	..	9	...	8.0	5.9	1.0	
28	1370	1170	161	206	7	48	17	9	...	8.0	6.0	1.0	
29	1270	1400	161	189	7	48	22	9	...	8.0	6.2	1.0	
30	1370	1200	161	175	7	48	..	9	...	8.0	6.8	1.0	
31	1370	940	161	137	7	48	19	9	...	8.0	4.7	1.0	
32	1460	720	161	205	7	48	34	9	...	8.0	6.8	1.0	
33	1470	1300	161	182	7	48	43	9	...	8.0	7.3	1.0	
79	980	780	159	162	15	50	41	10	144	8.3	8.5	1.1	
80	830	540	159	106	15	50	33	10	113	8.3	6.2	1.1	
81	780	600	159	127	15	50	32	10	121	8.3	6.4	1.1	
82	1330	540	159	101	15	50	35	10	105	8.3	6.6	1.1	
83	1180	525	159	111	15	50	28	10	105	8.3	5.5	1.1	
84	1270	1070	164	171	8	65	41	10	159	9.5	6.6	0.9	
85	930	1070	164	150	8	65	43	10	152	9.5	8.6	0.9	
86	780	630	164	59	8	65	22	10	53	9.5	2.1	0.9	
87	1280	1000	164	181	8	65	75	10	187	9.5	8.4	0.9	
88	730	810	164	125	8	65	41	10	113	9.5	6.2	0.9	
89	1180	810	154	124	10	65	41	12	113	9.2	6.2	1.3	
90	970	750	154	81	10	65	37	12	76	9.2	4.3	1.3	
91	730	1100	154	132	10	65	44	12	170	9.2	5.7	1.3	
92	930	615	154	94	10	65	34	12	104	9.2	4.8	1.3	
93	580	1310	154	199	10	65	54	12	174	9.2	7.3	1.3	
94	1290	620	154	65	10	66	58	12	80	8.9	5.2	1.3	10
95	1070	700	154	60	10	66	55	12	74	8.9	10.8	1.3	10
96	970	700	154	61	10	66	54	12	74	8.9	6.3	1.3	10
97	1170	900	154	92	10	66	66	12	107	8.9	7.9	1.3	10
98	905	510	154	62	10	66	28	12	74	8.9	2.6	1.3	10
99	1620	650	158	59	10	56	45	12	87	9.1	4.8	1.3	10
100	730	1325	158	182	10	56	70	12	200	9.1	6.7	1.3	10

TABLE I—(Continued)

Day	Fluid Intake (ML.)	Urine Volume (ML.)	Sodium (mEq.)			Potassium (mEq.)			Chloride (mEq.) Urine	Nitrogen (Gm.)			DCA* (Mg.)
			Diet	Urine	Fecal	Diet	Urine	Fecal		Diet	Urine	Fecal	
101	1770	...	158	...	10	56	...	12	...	9.1	...	1.3	10
102	930	1250	158	174	10	56	33	12	163	9.1	5.5	1.3	10
103	970	1125	158	128	10	56	51	12	132	9.1	5.6	1.3	10
104	930	1150	167	165	6	69	34	8	150	9.5	5.7	1.1	
105	1130	1150	167	167	6	69	33	8	135	9.5	6.3	1.1	
106	930	1100	167	186	6	69	33	8	178	9.5	6.6	1.1	
107	1170	1275	167	208	6	69	43	8	...	9.5	6.3	1.1	
108	1210	1310	167	210	6	69	41	8	206	9.5	6.1	1.1	
109	1220	1400	170	183	6	80	47	15	184	10.5	5.2	1.4	
110	1400	1160	170	128	6	80	56	15	124	10.5	6.8	1.4	
111	1270	1250	170	118	6	80	70	15	139	10.5	3.2	1.4	
112	1220	1000	170	111	6	80	77	15	112	10.5	4.8	1.4	
113	880	...	170	...	6	80	...	15	...	10.5	...	1.4	
114	1180	1000	145	124	5	65	52	11	120	9.7	6.8	1.3	
115	1170	1000	145	138	5	65	63	11	136	9.7	7.8	1.3	
116	930	600	145	104	5	65	42	11	103	9.7	4.8	1.3	
117	1260	950	145	143	5	65	38	11	122	9.7	5.0	1.3	
118	830	860	145	101	5	65	60	11	100	9.7	5.7	1.3	

* Desoxycorticosterone acetate.

TABLE II
EFFECT OF DCA ON EXCRETION OF CREATINE (SUBJECT B. R.†)

Time (Min.)	Urine Flow (Ml./min.)	Mannitol Clearance (Ml./min.)	Mannitol U/P*	Creatine			Creatine Mannitol Clearance Ratio
				Serum (Mlg. %)	Urine (Mg. %)	Clearance (Ml./min.)	
I. Before Administration of DCA †							
0	Mannitol, 20 Gm. in 80 ml., single injection I. V.						
9	Creatine, 25 Gm. by mouth in 440 ml. water,						
27	2.4	46.7	19.4	3.2	24	17.8	0.38
47	2.6	54.0	20.9	9.5	135	37.0	0.68
69	3.4	52.7	15.7	24.0	261	37.0	0.70
90	4.3	42.9	10.0	28.7	221	33.1	0.79
II. On 17th Day of DCA Administration (First Course)							
0	Mannitol, 20 Gm. in 80 ml., single injection I. V.						
17	Creatine, 25 Gm. by mouth in 440 ml. water						
41	5.7	65.9	11.6	9.1	110	68.7	1.04
63	11.5	80.5	7.0	18.5	143	88.0	1.09
88	3.5	48.2	13.8	24.3	306	44.5	0.93

* Urine mannitol concentration/serum mannitol concentration.

† Desoxycorticosterone acetate.

‡ Surface area: 1.68 sq. m.

After six to ten days of continuous treatment with DCA, changes in the movement of electrolytes and water occurred. Sodium excretion increased above control levels, ultimately producing a strongly negative sodium balance which was not reversed by

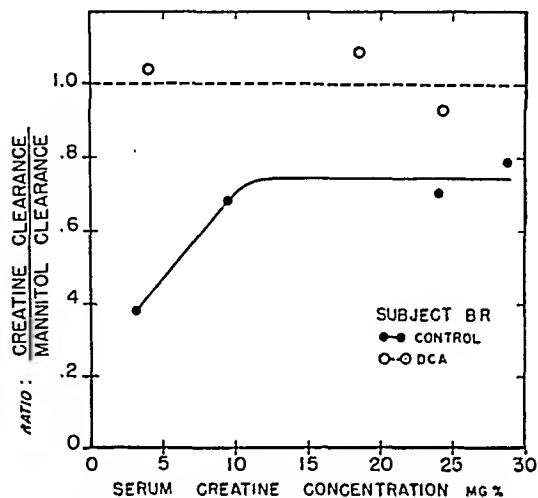


FIG. 2. Renal tubular reabsorption of creatine before and during administration of DCA. Reabsorption is a function of the ratio of creatine clearance to glomerular filtration (mannitol clearance). Note that during DCA treatment the ratio approximated 1.0 indicating that creatine was not reabsorbed.

augmenting dietary sodium. Chloride moved with sodium; the potassium balance became negative. There was a mild diuresis and, despite an increase in voluntary water intake, the difference between intake and urine output was decreased. Body weight decrease was commensurate with loss of water. No changes in muscle strength or in degree of myotonia were observed.

During the first five to ten days following withdrawal of DCA negative sodium balance persisted. There was an immediate marked potassium retention which diminished to normal balance over a ten-day period. Diuresis and augmented water intake continued as long as sodium was being lost. Decrements in body weight paralleled those of water balance. Following the first course of DCA there was a brief increase in nitrogen balance. This phenomenon did not occur during recovery from the second course of DCA.

The concentration of sodium in the serum rose to 148 mEq./L. during the early days of DCA administration and fell during the period of diuresis to 136 mEq./L. Serum potassium concentration decreased but remained within the accepted normal range. It is of interest to note that the patient complained spontaneously that his food tasted excessively salty at the time the serum sodium concentration was highest and that this complaint ceased during the period of diuresis.

As in experiments with the dog,¹⁹ the glomerular filtration rate was uninfluenced by prolonged DCA administration. Urine flow was augmented and the ratio of urine mannitol concentration to serum mannitol concentration was decreased, indicating diminished water reabsorption by the renal tubule. Reabsorption of creatine by the renal tubules was blocked completely by DCA even at low serum creatine concentration. (Table II, Fig. 2.)

During the periods of DCA administration arterial systolic pressure tended to increase (range, 118 to 144 mm. Hg) above the control range (112 to 120 mm. Hg). Arterial diastolic pressure (70 to 84 mm. Hg) did not change. No modification of the concentrations of blood glucose or non-protein nitrogen occurred.

COMMENTS

The response to DCA elicited in a patient with myotonic dystrophy, a disease characteristically associated with testicular atrophy and possibly with derangement of other endocrine glands, may not represent the response to be expected in normal man. Nevertheless, the evidence in this patient indicated that corticoadrenal function was normal with respect to electrolyte economy prior to DCA administration. The effects of DCA administration in our subject may be divided for purposes of analysis into the early, late and withdrawal phases.

The early effects are the familiar ones described in normal man by Thorn and Emerson¹⁵ and qualitatively resemble the effects of DCA treatment of patients with

Addison's disease and of adrenalectomized animals: sodium, chloride and water retention, potassium loss and weight gain.^{4,9,16,17,18}

The late effect on water metabolism in the subject herein described resembles that seen in the normal dog subjected to a similar regimen. The mechanism responsible for DCA-induced diuresis remains a matter of speculation. Ragan et al.¹² suggest that polyuria in the dog under these circumstances is secondary to polydipsia. These workers observed that in the dog, in which the syndrome of polyuria and polydipsia had been established by large doses of DCA, water restriction caused a rise in serum sodium concentration and a fall in urine volume. Although our patient complained of thirst during the early phase of DCA administration and subsequently voluntarily increased his water intake, most of the data at hand point toward a primary renal mechanism. The composition of the urine was unlike that described in water diuresis in which urine is dilute with respect to chloride^{8,20} and presumably with respect to sodium. Despite the moderate diuresis occurring during DCA administration the urinary concentrations of sodium, chloride and potassium increased. (Table 1.) Creatinuria cannot be increased by forced water diuresis,²¹ a fact which renders it improbable that accelerated urine flow was primarily responsible for the reduction in tubular capacity for reabsorbing creatine. For these reasons it is unlikely that enhanced water intake is the primary mechanism responsible for the syndrome. Increased excretion of sodium, chloride, potassium, water and creatine suggests that widespread inhibition of certain renal tubular reabsorptive functions may have taken place.

When DCA is withdrawn, the pattern of electrolyte balance (sodium, chloride and water loss, marked potassium retention) resembles that of patients with Addison's disease and suggests that some hypofunction of the adrenal cortex has been induced. That corticoadrenal atrophy can be produced by DCA has been demonstrated anatomically.^{2,13,14} Fortunately, the evidence of

reduced corticoadrenal function in this patient did not persist beyond ten days.

The possibility that atrophy so induced may not be regularly reversible has discouraged us from inquiring in normal man into the cause of the inhibition of renal tubular reabsorption associated with prolonged exhibition of DCA.

It is of interest that dogs in which polyuria was induced by DCA developed weakness associated with loss of muscle potassium.³ The subject observed here showed no such impairment of motor power. The discrepancy may be due to the fact that the doses of DCA were smaller in man (0.08 to 0.25 mg./Kg.) than in the dog (1.6 mg./Kg.) and that administration of DCA was terminated in order to avoid loss of potassium sufficient to produce serious derangement of the intracellular electrolyte pattern.

The assumption has been made that this subject responded to DCA in a manner which represents the normal. This may be proved subsequently to be untenable. His response to DCA may be related to his underlying myotonic dystrophy although evidence for this is lacking.

SUMMARY

1. Two courses of DCA, in doses varying from 5 to 15 mg. a day, were given to a patient with myotonic dystrophy.

2. During the second week of DCA administration there was an increase in voluntary fluid intake, a diuresis with reduction in water balance, negative sodium and potassium balances and loss of body weight. The glomerular filtration rate was unchanged. Reabsorption of water and of creatine was inhibited.

3. During the week following withdrawal of DCA, after polydipsia, polyuria and electrolyte loss had been established, the pattern of electrolyte balance resembled that of Addison's disease.

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Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions*

J. V. WARREN, M.D., E. S. BRANNON, M.D., H. S. WEENS, M.D.

and E. A. STEAD, JR., ** M.D.

Atlanta, Georgia

MANY observations on the effects of decreasing the blood volume in man have been reported, but much less information is available on the effects of increasing the blood volume. It is known that an increase in blood volume caused by the rapid intravenous administration of fluid will produce a rise in venous pressure. The effects of this rise in venous pressure on the cardiac output and the size of the heart are of considerable importance to the physician. If, as the venous pressure rises, the normal heart is dilated and the cardiac output greatly increased, this would indicate that a considerable strain was being placed upon the heart. Such a reaction might explain the poor tolerance of patients with heart failure to intravenous fluids.

METHODS

Normal young volunteer subjects were used for the various studies. Blood volume changes were produced by the rapid intravenous administration of fluids through a No. 17 gauge needle in an antecubital vein. The rate of infusion varied from 32 to 77 cc. per minute. Physiological saline solution and 5 per cent human serum albumin†

† The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross and the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

* From the Departments of Medicine and Roentgenology, Emory University Medical School, and the Medical and Roentgenological Services, Grady Hospital, Atlanta, Ga.

** Present address: Department of Medicine, Duke University, Durham, N. C.

in physiological saline solution were used. All studies except those relating to heart size were carried out under basal conditions. The subjects in all instances remained in the horizontal position for at least thirty minutes prior to any observations.

The right atrial pressure was measured by means of a water manometer attached to a catheter extending through the venous system to the right atrium.^{1,2} A point 5 cm. below the fourth right costochondral junction was used as the reference point. Cardiac output determinations were carried out utilizing the direct Fick principle.^{1,2} In most instances the arterial pressure was recorded from the femoral artery by the method of Hamilton.³ Heparin was used as the anticoagulant in the hematocrit tubes. Plasma proteins were determined by the falling drop method.⁴ Hemoglobin content of the blood was measured as oxyhemoglobin in an alkaline solution by means of a photoelectric colorimeter. Plasma volume was determined in a few instances by means of the blue dye T 1824. In the remainder, the changes in blood volume were calculated from changes in hematocrit reading assuming a normal initial blood volume based on surface area.

The studies on heart size were carried out at another time; teleoroentgenograms were made of the heart with the subject in the horizontal position. The transverse diameter of the heart, determined from these films,

was used as a measure of heart size. Care was taken to have the position of the diaphragm at nearly the same level for each film.

RESULTS

Ten normal subjects received intravenous infusions of physiological saline solution varying in amount from 750 to 1,825 cc. The infusions were given at a rate of 43 to 77 cc. per minute. Before the infusions were started, control measurements were made. Additional observations were made soon after completion of the intravenous infusion and usually some time later when a major portion of the infused fluid had left the vascular system. These data are recorded in Table I.

Seven other subjects received 1,000 cc. of physiological saline solution containing 50 Gm. of albumin. This produced a relatively isotonic and isoncotic fluid. These data are recorded in Table II.

Two subjects received 1,000 cc. of albumin solution and x-ray studies of the heart size were made. The transverse diameter of the heart was measured on both control and postinfusion films.

There was no evidence that rapid intravenous infusions given at the rate used in the present studies overloaded or adversely affected the circulation. The initial effects of the saline and albumin solutions were essentially the same. They differed in that the saline solution left the vascular system rapidly, whereas the albumin-containing fluid remained in the vascular system for a longer period of time. The infusion produced no symptoms. The neck veins became visible as the venous pressure rose; there was no change in skin color.

In all instances the infusions caused an increase in plasma volume demonstrated either by fall in the hematocrit reading or by actual measurements of the plasma volume by the dye technic. With the saline

solution there was also a change in plasma protein concentration. The increase in plasma volume following saline solution was relatively smaller and less prolonged than that following albumin solution.

In all instances there was an elevation of the central venous (right atrial) pressure. This varied from 30 to 95 mm. of water following saline solution and from 60 to 130 mm. of water following albumin solution. Other observers have noted similar changes.^{5,6} The rise in atrial pressure appears to represent merely the greater filling of the vascular system with a general elevation of pressure and consequent distention of the least rigid parts. This is similar to the rise in static venous pressure in patients with congestive failure described by Starr.⁷

The cardiac output was measured before and after infusions in all subjects. The infusions produced somewhat variable responses. The changes in cardiac output bear no direct relationship to elevation in the right atrial pressure nor any other observed function of the cardiovascular system. The importance of making observations before, during and after the administration of fluid is emphasized by the study of the data recorded here. If the subject is apprehensive before the fluid is given and becomes more relaxed during the procedure, the cardiac output will fall; if he is relaxed at the beginning of the study and becomes restless as the observations are continued, the cardiac output will rise. These changes are not related to the changes in atrial pressure caused by the increased blood volume. This can be demonstrated by a third determination after the atrial pressure has fallen toward the control level. Results similar to ours following infusion of the albumin solution have been obtained in another laboratory in this country.⁸ Other observers have found a moderate change in cardiac output proportional to the change in the right atrial pressure.⁹ We are unable to explain the

TABLE I

NORMAL SUBJECTS RECEIVING PHYSIOLOGICAL SALINE SOLUTION

Patient	Remarks	Rate of Injection	Surface Area	Oxygen Consumption	A-V Oxygen Difference	Cardiac Index	Hematocrit Reading	Hemoglobin	Total Protein	Arterial Pressure			Pulse Rate	Atrial Pressure
										Systolic	Diastolic	Mean		
		Cc. per Min.	Sq. M.	Ml. per Min. per Sq. M.	Vol. per Cent	Liters per Min. per Sq. M.		Gm. per 100 Ml.	Gm. per 100 Ml.	Mm. Hg			Beats per Min.	Mm. H ₂ O
1	Before saline.	43	1.79	116	2.3	5.0	32	9.8	5.8	155	80	110	100	5
	After 1,000 cc. saline.	137	2.2	6.3	28	9.0	5.0	158	80	109	88	65
	66 min. later.	106	2.8	3.8	29	9.2	5.3	150	76	103	84	30
2	Before saline.	67	1.88	119	4.2	2.8	49	15.1	8.9	125	69	90	60	10
	After 1,000 cc. saline.	110	3.3	3.2	45	13.9	7.8	124	66	85	57	40
	34 min. later.	121	3.7	3.3	46	14.2	8.0	114	61	80	57	5
3	Before saline.	53	1.77	157	3.9	4.0	43	12.9	6.4	106	62	78	82	35
	After 1,000 cc. saline.	157	3.9	4.0	40	11.9	5.5	107	64	78	84	95
	45 min. later.	147	4.5	3.3	42	12.2	5.8	113	70	83	84	50
4	Before saline.	59	1.69	117	4.5	2.6	43	12.8	5.5	129	79	96	88	-15
	After 1,825 cc. saline.	111	2.3	4.8	38	10.5	4.3	149	85	107	71	30
	35 min. later.	134	3.8	3.5	39	11.4	4.8	143	88	109	79	-5
5	Before saline.	65	1.69	107	4.0	2.7	38	11.3	5.7	108	57	75	79	15
	After 1,300 cc. saline.	116	3.3	3.5	33	9.6	4.6	116	62	84	75	45
	45 min. later.	119	3.9	3.1	35	9.9	5.0	121	66	87	68	30
6	Before saline.	77	1.82	134	2.7	4.9	45	14.1	6.6	106	60	76	68	50
	After 1,000 cc. saline.	132	3.6	3.7	40	11.8	5.3	111	60	78	70	110
	28 min. later.	126	3.2	4.0	42	12.9	6.1	109	60	79	68	65
7	Before saline.	53	2.23	93	4.1	2.3	37	12.8	6.4	81	-25
	After 1,000 cc. saline.	83	3.5	2.4	32	11.3	4.9	74	55
8	Before saline.	59	1.81	142	3.4	4.2	41	12.7	6.4	104	5
	After 1,000 cc. saline.	162	4.9	3.3	38	11.2	5.6	119	67	86	107	80
9	Before saline.	67	1.64	104	4.2	2.5	35	9.8	7.3	122	78	...	75	-25
	15 min. after 1,000 cc. saline.	130	4.1	3.2	30	8.5	5.1	68	70
	11 min. later.	117	4.3	2.7	31	8.7	5.8	63	0
10	Before saline.	62	1.75	130	4.6	2.9	34	10.9	5.8	112	60	77	62	-5
	After 750 cc. saline.	125	4.5	2.7	31	10.1	4.8	120	63	82	54	65
	35 min. later.	138	5.4	2.6	34	10.7	5.1	57	15

variance of these findings from ours; in both, the cardiac output was determined by the method of right heart catheterization.

tion in the pulse rate.¹⁰ The arterial pressure showed slight, apparently random, variations. Oxygen consumption and arterio-

TABLE II
NORMAL SUBJECTS RECEIVING 1,000 CC. OF 5 PER CENT HUMAN ALBUMIN IN PHYSIOLOGICAL SALINE SOLUTION

Patient	Remarks	Rate of Injection	Surface Area	Oxygen Consumption	A-V Oxygen Difference	Cardiac Index	Hematocrit Reading	Hemoglobin	Total Protein	Arterial Pressure			Pulse Rate	Atrial Pressure
										Systolic	Diastolic	Mean		
		Cc. per Min.	Sq. M.	Ml. per Min. per Sq. M.	Vol. per Cent	Liters per Min. per Sq. M.		Gm. per 100 Ml.	Gm. per 100 Ml.	Mm. Hg			Beats per Min.	Mm. H ₂ O
11	Before albumin.....	56	1.95	116	3.3	3.5	41	14.5	6.0	127	69	91	65	40
	After albumin.....	108	3.5	3.0	36	12.2	5.7	120	68	87	73	110
	70 min. later.....	133	3.3	4.0	39	12.7	5.9	75
12	Before albumin.....	63	1.69	151	3.5	4.3	45	5.9	110	65	81	100	15
	After albumin.....	170	3.7	4.6	37	5.6	113	65	80	103	120
13	Before albumin.....	63	1.61	117	3.4	3.4	34	10.0	7.2	136	78	98	94	-15
	After albumin.....	119	3.0	3.9	27	8.8	6.7	127	72	92	94	45
	55 min. later.....	137	3.0	4.6	28	8.9	6.8	140	80	100	84	15
14	Before albumin.....	32	2.0	127	3.6	3.6	46	14.2	6.8	125	75	88	88	-15
	After albumin.....	129	2.2	5.9	36	11.8	6.2	149	79	103	79	95
	55 min. later.....	111	2.5	4.4	39	12.6	6.5	155	79	103	60	+30
15	Before albumin.....	63	1.73	142	5.6	2.5	43	14.8	5.5	119	68	83	53	60
	After albumin.....	130	3.9	3.3	33	11.5	5.0	142	75	99	60	190
	60 min. later.....	124	4.0	3.1	37	13.8	5.6	142	78	98	52	90
16	Before albumin.....	37	1.73	129	4.2	3.1	38	12.7	5.9	163	86	113	66	20
	After albumin.....	121	2.4	5.1	29	10.0	5.5	166	84	113	66	90
	60 min. later.....	120	2.3	5.2	32	10.4	5.8	150	77	105	60	50
17	Before albumin.....	37	1.74	120	2.6	4.6	32	9.5	6.1	107	47	66	60	5
	After albumin.....	127	4.9	2.6	27	8.1	6.2	107	47	69	71	105
	100 min. later.....	118	7.8	6.4	45

The majority of the data given in this table appeared in an article on shock in the *Archives of Internal Medicine*, 77: 564, 1946.

The intravenous infusions produced little change in the pulse rate. This is in contrast to the effect of removing blood from the vascular system where the lowered atrial pressure is often accompanied by an eleva-

tion in the pulse rate.¹⁰ The arterial pressure showed slight, apparently random, variations. Oxygen consumption and arterio-

venous difference of mixed venous blood were not significantly altered.

In two patients x-ray studies of the transverse diameter of the heart were made with the patient in a horizontal position. Venous

tourniquets were applied to the thigh and inflated to the level of the diastolic pressure. After five minutes control films were taken. The venous tourniquets were released and the albumin solution was given rapidly. The average increase in blood volume produced by the albumin as calculated from the hematocrit readings was 1,000 cc. Repeat x-ray studies were made. From previous observations¹⁰ it is known that the venous tourniquets lower the right atrial pressure an average of 45 mm., and the rapid administration of 1,000 cc. of 5 per cent albumin solution raises it an average of 80 mm. Thus, the change in right atrial pressure between the two sets of roentgenograms was approximately 125 mm. of water. No change in the size of the heart could be detected.

COMMENTS

The original stimulus to carry out the studies reported here was derived from observations on the hemodynamics of hemorrhage in man.¹¹ Hemorrhage causes first, a fall in atrial pressure and later a decrease in cardiac output and the clinical picture of shock. It soon became obvious that in the patients admitted with acute hemorrhage there was no absolute level of cardiac output at which the clinical symptoms of shock appeared. The absolute figure for cardiac index (output per sq. m. of surface area) had to be interpreted in the light of the requirements of the body for blood flow. A cardiac index of 3 might be adequate for one patient but grossly inadequate for another. The response to increasing the blood volume was used as a guide to determine whether the cardiac output was adequate. If a rise in atrial pressure caused a rise in cardiac output, it was believed that the increase in blood volume had been beneficial. This interpretation would not be valid if the cardiac output increased in normal subjects as the atrial pressure rose.

The evidence presented here, plus that obtained in the study of patients in shock, demonstrates that a rise in atrial pressure above the normal level will not consistently cause an increase in cardiac output. Hardy and Godfrey,¹² using the ballistocardiograph, found that the intravenous infusion of physiological saline solution caused an increase in cardiac output in patients who were dehydrated but produced no change in normally hydrated subjects. The important clinical implication is that a moderate increase in blood volume above the normal level in patients with shock will not place an added mechanical burden upon the heart. If factors are present which tend to cause fluid to localize in the lungs, the excess fluid may cause acute pulmonary edema even though heart failure does not occur.

Rather abrupt changes in the heart size are noted clinically in many conditions. Those occurring in patients with Addison's disease, arteriovenous fistula and following fever therapy are examples. Several explanations for these changes have been offered; one is that it is a reflection of a change in blood volume. The observations on heart size reported here demonstrate that an increase in blood volume of approximately 1 liter and a change in atrial pressure of approximately 125 mm. of water produce little change in the heart size of normal subjects. It must be remembered, however, that this increase in blood volume is not accompanied by a significant change in extracellular fluid volume.

The data reported here give further evidence that in normal subjects a large increase in blood volume causes no evidence of circulatory embarrassment. The most striking change was the rise in right atrial pressure. This is not interpreted as a sign of cardiac failure. The hearts in these subjects were normal and capable of large increases in cardiac output. If the fluids had induced heart failure, an actual fall in

cardiac output would have been expected. If the tone of the vascular bed is increased by sympathicomimetic drugs, the pressure in the venous system will rise without any evidence of heart failure.¹³ It appears that in normal subjects the elevation of venous pressure caused by increasing the blood volume or increasing the tone of the vascular bed cannot be interpreted as evidence of heart failure.

These experiments in normal subjects might at first sight appear to be at variance with common clinical experience in patients, particularly those with heart disease. Often in such patients intravenous infusions are not well tolerated and from time to time precipitate an attack of acute pulmonary edema. It is usually stated that the fluids, by raising the venous pressure, increase the work of the heart. The observation that raising the venous pressure fails to increase the output of a normal heart does not support such a belief. It appears probable that no increased burden of work is actually added to the heart. This concept is further supported by observations in this laboratory on venesection in two patients with chronic congestive failure. Sudden lowering of the venous pressure produced no fall in cardiac output. The clinical evidence still remains, however, that venesection may help and fluids may harm patients with cardiac failure. Other factors, therefore, must be operative.

It would appear that those factors responsible for the gradual development of pulmonary edema in the natural history of heart failure are responsible for the dramatic precipitation of the edema by the infusion. The patient with heart failure retains salt and water. This is another way of saying that the fluid intake exceeds the fluid output. A large portion of the retained salt and water accumulates in the lungs and is the primary factor in reducing the vital capacity. At this time it is not necessary to discuss

the factors leading to the localization of fluid in the lungs; it is sufficient to emphasize that this localization of fluid is very common. When physiological saline solution is given intravenously at a rate which exceeds its excretion by the kidneys, those factors already tending to localize fluid in the lungs remain operative and a large portion of the added fluids pass into lungs already moderately edematous and cause an attack of frank pulmonary edema. Once the lungs have become sufficiently edematous, the final episode of severe dyspnea and production of frothy sputum may be accompanied by restlessness and anxiety, resulting in an increase in cardiac output and trapping of an additional few hundred cc. of blood behind an inadequate left ventricle.

These observations re-emphasize the fact that the rise in systemic venous pressure itself is not an important factor in producing dyspnea. The increase in venous pressure produced in normal subjects was much greater than those occurring in many cardiac patients who developed frank pulmonary edema from the intravenous administration of fluid. It has been demonstrated, however, that for a given rate of infusion the venous pressure may rise more rapidly in certain patients with cardiac failure than in normal subjects.⁵ This is explained by several factors. The circulation in patients with cardiac failure may be inadequate although the patient is at rest; hence, the flow of blood to the tissues is diminished. They are less able to distribute the fluid throughout the body so that loss from the vascular system is delayed. In addition, such patients may already have sub-clinical retention of extracellular fluid; therefore, slight additions may completely fill the space normally available for the deposition of the injected fluid. Similarly, the blood volume may be somewhat increased before the infusion is begun even though the venous pressure is within normal limits. All of these

factors tend to result in a rapid increase in plasma volume when the infusion is started and the venous pressure may rise rapidly.

We believe that it is the fluid which leaves the blood stream and enters the lungs which causes the difficulty, and that a rise in venous pressure or a fall in the serum protein level is dangerous only when local factors in the lungs cause a disproportionate amount of the excess fluid to accumulate. The fact that the lungs are wet is an indication that certain factors are operative to cause a selective localization of retained fluid in the lungs. There is some additional clinical and experimental evidence to support this view. Dogs given large quantities of physiological saline develop massive generalized edema without obvious dyspnea.¹⁴ Patients with nephrosis and cirrhosis develop marked edema without conspicuous pulmonary edema until heart failure intervenes. A patient with cardiac failure and an inadequate cardiac output who has dry lungs resulting from a regimen of salt restriction and administration of mercurial diuretics will tolerate intravenous fluids well. This same patient after a few days of a high salt diet may develop frank pulmonary edema during the administration of intravenous fluids.

Why does the fluid tend to accumulate in the lungs to such a striking degree in those patients with heart failure? If physiological saline solution is given to a normal subject at a rate which exceeds his ability to excrete fluid by the kidneys, many of the phenomena of congestive failure occur. He develops increased venous pressure and generalized edema but the early water-logging of the lungs so characteristic of congestive failure is lacking. The hypothesis of left ventricular failure with an increase in pulmonary capillary pressure is still an attractive explanation to account for the difference in response of normal subjects and those with heart failure. If the pul-

monary capillary pressure were increased above the normal level by damming back of blood behind the left ventricle it would explain why so much of retained salt and water accumulate in the lungs. If the pulmonary edema results from a high pulmonary capillary pressure plus retention of salt and water by the body, it would explain the observed facts that either causing the body to lose salt and water by the administration of diuretics or improving the circulation by the use of digitalis lessens the pulmonary congestion.

SUMMARY AND CONCLUSIONS

1. The effect of increasing the blood volume by the intravenous administration of 5 per cent albumin solution and physiological saline solution was studied.
2. The increase in blood volume consistently caused a rise in atrial pressure. The cardiac output, arterial blood pressure and pulse rate showed no consistent change.
3. Variations in atrial pressure of approximately 125 mm. of water produced no demonstrable change in the transverse diameter of the heart.
4. Increasing the blood volume and atrial pressure throws no demonstrable mechanical burden on the circulation in normal subjects. It is suggested that this may also be true in patients with heart failure. Acute pulmonary edema is precipitated by the intravenous administration of fluids in patients with heart failure because certain factors are operative to cause a large portion of the administered fluid to accumulate in lungs already moderately edematous.

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Value and Limitations of the Thymol Turbidity Test as an Index of Liver Disease*

HENRY G. KUNKEL, M.D.

New York, New York

A NUMBER of reports have appeared in recent literature demonstrating the value of the thymol turbidity test in the diagnosis of liver disease.¹⁻⁷ A close correlation with the cephalin flocculation reaction was observed although certain definite discrepancies were noted.^{4,5,8} The thymol turbidity test has the advantage of being extremely simple to perform and of furnishing accurate and reproducible values. Certain information has also been obtained regarding factors in the serum of patients with liver disease responsible for a positive reaction.⁹⁻¹² Serum lipids and lipoprotein complexes migrating electrophoretically in the beta globulin fraction were found to play an essential rôle in the reaction. The degree of elevation of the gamma globulin fraction was also found to be important. In acute infectious hepatitis values for the thymol turbidity test were found to reflect both the elevation in serum lipids and the increase in the globulin fraction.

The purpose of the present report is to present certain clinical observations on the value and limitations of the thymol turbidity test and to attempt to explain the results in terms of aberrations in the serum responsible for the reaction. Emphasis was placed on the study of results of the test in disease states which are characterized by a high globulin level of the serum.

In view of the observations previously reported⁸ showing that maximal values for the thymol turbidity test may not be reached until after the acute symptomatic phase of infectious hepatitis is over, it was thought to be important to do serial determinations throughout the course of other diseases

before drawing conclusions concerning the variation in thymol turbidity reaction. The results presented in this study represent the maximal aberrations found in various conditions as a result of serial determinations.

MATERIAL AND METHODS

The thymol turbidity test was carried out by the method of MacLagan¹ modified for the Coleman Jr. spectrophotometer.² The standard used was prepared as follows: 3 cc. of a BaCl_2 solution (containing 1.15 Gm. $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ per 100 cc.) is made to 100 cc. in a volumetric flask with 0.2 N H_2SO_4 . This BaSO_4 suspension gives a turbidity equivalent to 20 units. By assigning the value 20 units to the optical density reading obtained in a colorimeter or a spectrophotometer at 650 μ , with the BaSO_4 suspension, a standard curve can be constructed by drawing a line through the point obtained in the above manner and the 0 point on ordinary graph paper. The type of cuvette is not important as long as the same type is used for constructing the standard curve as for routine readings. This curve gives values somewhat higher than those found in other laboratories but, since the normal range was still found to be below 5 units, it was believed that the greater spread of values for positive sera aided in the interpretation of the results. Other liver function tests were performed in the manner described in a previous communication.⁶ Determinations were carried out on the sera of patients admitted to the Out-patient Department and the Hospital of The Rockefeller Institute. A few patients in other hospitals in the New York area were also studied. Sera from certain patients with tropical diseases were obtained from various Army hospitals throughout the country.

* From the Hospital of The Rockefeller Institute for Medical Research.

THE THYMOL TURBIDITY TEST IN DISEASES OF THE LIVER

Evidence that a positive thymol turbidity test is an indication of active liver disease was obtained from a study of the results of

TABLE I
COMPARISON OF THE RESULTS OF THYMOL TURBIDITY DETERMINATIONS IN CASES OF INFECTIOUS HEPATITIS AND IN NORMAL CONTROLS OF THE SAME AGE

No. of Cases	Maximal Values Reached during the Disease		
	Highest	Lowest	Average
76	41 units	8 units	23 units

No. of Cases	Values Obtained in Normal Individuals		
	Highest	Lowest	Average
46	5 units	0.5 units	3.0 units

this test in infectious hepatitis. Table I shows observations on a group of Navy patients with acute infectious hepatitis who were admitted to The Rockefeller Institute Hospital within the first ten days of their illness. It can be seen that every one of these patients showed higher values for the thymol turbidity test than the highest value obtained in the normal control group.

The degree of elevation in acute hepatitis was variable and did not correspond to the severity of the illness. The data in Table II demonstrate that although the average maximal bilirubin values are usually proportional to the severity of clinical symptoms, the values for the thymol turbidity test show no such relationship. In fact, the group of patients exhibiting the most severe symptoms showed a slightly lower average maximal value for the thymol turbidity test than did patients in the other three groups with less severe symptoms of the disease. It appears, therefore, that although a positive reaction is associated with acute liver

disease, the degree of turbidity is not a reflection of the severity of the liver damage.

In an investigation of a family epidemic of infectious hepatitis⁵ opportunity was afforded to study several very mild non-icteric cases. The thymol turbidity test was

TABLE II
COMPARISON OF THE AVERAGE MAXIMAL VALUES OBTAINED DURING THE COURSE OF INFECTIOUS HEPATITIS FOR THE THYMOL TURBIDITY AND THE PLASMA BILIRUBIN IN PATIENTS GROUPED ACCORDING TO THE SEVERITY OF THE SYMPTOMS OF THE DISEASE

Severity of Symptoms	No. of Cases	Average Maximal Values Reached during the Course of the Disease	
		Bilirubin	Thymol Turbidity
++++	11	9.2	18.6
+++	22	8.5	24.0
++	18	4.6	23.0
+	16	3.2	19.0

found to be a more sensitive indicator of the presence of the disease than any other test that could be applied. In addition, it usually remained positive for at least six weeks enabling one to make the diagnosis several weeks after all other clinical and laboratory indications of the disease had disappeared. This served to emphasize the value of the test for epidemiologic surveys.

The thymol turbidity test was also found to be of use in anticipating relapses of infectious hepatitis.⁶ When serial determinations showed persistently high values during convalescence, the possibility of relapse could be strongly suspected and such patients could be returned to bed rest and dietary therapy before serious results ensued.

One of the chief uses of the thymol turbidity test was in the evaluation of mild, persistent symptoms following an attack of infectious hepatitis. The data of Table III show that in a group of service men observed more than six months after an attack of infectious hepatitis this test proved to be positive in 70 per cent of the men showing mild symptoms and in only 12 per cent of

the group who were symptom-free. It was positive more often than any other liver function test in this important group of patients who are so often diagnosed as psychoneurotic because the more commonly applied tests are negative. The other liver

with definite alterations in the albumin and total globulin of the plasma. It is evident that this test does not give a true indication of the degree of liver involvement in these patients. The patients with cirrhosis of the liver who did not give a history of alcoholism

TABLE III

VALUES FOR PLASMA BILIRUBIN, BROMSULFALEIN RETENTION, THE CEPHALIN FLOCCULATION REACTION AND THE THYMOL TURBIDITY REACTION IN PATIENTS SIX MONTHS OR MORE FOLLOWING AN ATTACK OF INFECTIOUS HEPATITIS

	No. of Cases	With Increased Plasma Bilirubin (Per Cent)	With Increased Bromsulfalein Retention (Per Cent)	With Positive Cephalin Flocculation Reaction (Per Cent)	With Increased Thymol Turbidity Values (Per Cent)
Persistent symptoms	40	45	48	50	70
No symptoms	34	15	0	12	12

function tests and blood constituents studied in these patients, in addition to those shown in Table III, included the bilirubin excretion test, the prothrombin time, the hippuric acid excretion test, the urine urobilinogen, the serum albumin and globulin and the ratio of free to total plasma cholesterol.

TABLE IV

RESULTS OF THYMOL TURBIDITY TEST DETERMINATIONS IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC CIRRHOSIS

	No. of Cases	Positive (Per Cent)	Highest Value, Units	Average Value, Units
Alcoholic cirrhosis	30	83	16	8.1
Non-alcoholic cirrhosis	24	96	36	16.7

In cirrhosis of the liver values for the thymol turbidity test proved to be considerably more variable than in infectious hepatitis. Table IV shows the results of this test in fifty-four patients with cirrhosis of the liver. The thymol turbidity test in patients whose liver disease was associated with chronic alcoholism and inadequate diet showed an average value of 8.1 units. Seventeen per cent of this group had normal values. These patients all had severe liver disease

showed a considerably higher average value for the thymol turbidity test. Five of the twenty-four patients in this group gave a definite history of infectious hepatitis in the past. In the remainder the etiology of the cirrhosis was obscure. Highest values were obtained in four cases of unusual cirrhosis associated with a globulin level of the serum above 6 Gm. per cent. Electrophoretic determinations demonstrated that the elevation in globulin was due entirely to an increase in the gamma globulin fraction.

THE THYMOL TURBIDITY TEST IN CONDITIONS OTHER THAN PRIMARY LIVER DISEASE

Table V summarizes the observations obtained in various disease states. For comparative purposes the value in normal patients and in those with liver disease were added. High values were found to be associated with the hyperglobulinemia found in various parasitic diseases, especially in kala azar. Here again the globulin aberration was almost entirely due to a rise in the gamma globulin fraction. In six patients with malaria that were studied a direct relation between the degree of elevation of values for the thymol turbidity test and the globulin level of the serum was present. This was also true in patients with typhus.

Serial determinations during the course of this disease revealed that values for the test showed a delayed rise and prolonged elevation which closely paralleled serum globulin changes. It appeared as if the thymol turbidity test merely reflected the globulin elevation in these acute infections.

TABLE V
COMPARISON OF MAXIMAL VALUES FOR THE THYMOL TURBIDITY TEST IN VARIOUS HEPATIC AND NON-HEPATIC DISEASES

	No. of Cases	Maximal Values Reached during the Disease	
		Highest	Average
Normal subjects	46	5.0	3.0
Infectious hepatitis	76	41	23.4
Alcoholic cirrhosis	30	16	8.1
Non-alcoholic cirrhosis	24	36	16.7
Kala azar	3	34	32.0
Typhus	6	16	12
Schistosomiasis	2	17	13
Malaria	6	19	15
Cinchophen poisoning	1	17	
CCl ₄ poisoning	1	7	
Obstructive jaundice	6	7	3.8
Hemolytic jaundice	4	3	2.4
Rheumatoid arthritis	7	12	4.0
Rheumatic fever	10	8.5	5.9
Bacterial pneumonia	5	6.5	4.6
Atypical pneumonia	14	10.8	5.9
Multiple myeloma	3	5.0	4.0
Nephrosis	5	5.0	2.0

In certain chronic diseases, however, such as rheumatoid arthritis and multiple myeloma, values for the reaction did not correspond to the marked hyperglobulinemia that was present in some of these patients. The globulin level was above 7 Gm. per cent in each of the patients with multiple myeloma and strongly positive results for the Takata-Ara and formol-gel reactions were obtained whereas the thymol test was consistently negative. Electrophoretic analysis of one of these sera demonstrated that the globulin aberration was due to a marked increase in the gamma globulin fraction.

A limited number of observations were made on the use of the thymol turbidity test in the differentiation of obstructive and

non-obstructive jaundice. Six jaundiced patients, who were later proven by operation or autopsy to have obstructive jaundice without histologic evidence of intrinsic parenchymal hepatic disease, all showed thymol turbidity values below 7 with an average value of 3.8 units. The lowest maximal value obtained in acute infectious hepatitis was 8 with an average of 23. It can be seen that this test alone may be of considerable value in differentiating the two conditions and when applied along with the alkaline phosphatase, cephalin flocculation and serum bilirubin, it becomes of particular value. Further observations are necessary to determine the effect of prolonged obstruction on the thymol turbidity reaction.

Four jaundiced patients who were later found to have familial hemolytic jaundice were sent to the Hospital of the Rockefeller Institute as cases of infectious hepatitis. The presence of normal values for the thymol turbidity test immediately initiated studies that led to the correct diagnosis.

Table v shows the average maximal values obtained during the course of three febrile diseases—rheumatic fever, pneumococcal pneumonia and atypical pneumonia. These patients showed a slight fall in the values for this test during convalescence. Atypical pneumonia was studied in considerable detail because an occasional patient showed values as high as 10 units during the early part of the disease.

Five patients with nephrosis and lipemic serum exhibited very high values for the thymol turbidity test as it is usually carried out. This was demonstrated to be a false positive reaction and by using a thymol solution with a high salt concentration in the control tube normal values for the test were obtained.⁹

RELATION OF THYMOL TURBIDITY TO CEPHALIN FLOCCULATION REACTION

Several observers^{3,4,6,8,12} have pointed out differences between the thymol turbidity and the cephalin flocculation reactions although it is generally agreed that the two tests bear a close resemblance. Table vi

shows the comparative results of four liver function tests in a mild case of acute infectious hepatitis. This case was of special value because determinations were obtained prior to the acute onset and during the pre-icteric stage of the disease. The close rela-

TABLE VI

COMPARISON OF SERIAL LIVER FUNCTION TEST DETERMINATIONS IN A MILD CASE OF ACUTE INFECTIOUS HEPATITIS OBSERVED DURING A FAMILY EPIDEMIC OF THIS DISEASE

Day of Disease	Bilirubin (Mg. Per Cent)	Brom- sulfalein Reten- tion at 45 Minutes (Per Cent)	Thymol Turbid- ity	Cepha- lin Floccu- lation
12 days prior to onset	0.4	2	1	0
2	0.6	30	3	++
5	1.0	31	12	++
7	2.3	34	16	++
12	1.3	11	21	++
19	0.5	3	22	+++
27	0.6	1	15	++
34	0.4	2	13	++
48	0.35	1	7	0

tionship between the thymol turbidity and cephalin flocculation reactions during convalescence is readily apparent especially in contrast with the more rapid fall in the plasma bilirubin and bromsulfalein retention levels. In all of the cases of infectious hepatitis studied this close relationship existed. It was brought out quite strikingly in the patients demonstrating low abnormal values for the thymol turbidity test. These patients also showed negative or weakly positive results for the cephalin flocculation reaction despite the fact that they often were quite ill and markedly icteric. The main difference demonstrated by the two tests in the study of infectious hepatitis was that the cephalin flocculation test became positive several days earlier than did the thymol turbidity reaction. This can be clearly seen from the patient described in Table VI and was observed in all of five patients who were tested early in the pre-icteric stage of the disease. It may be concluded that the ce-

phalin flocculation reaction is the more useful test during the pre-icteric stage of infectious hepatitis.

Both the cephalin flocculation and the thymol turbidity tests showed a prolonged elevation during convalescence from infectious hepatitis after signs and symptoms of the disease had ended and values for other liver function tests had returned to normal. It was here that the two tests paralleled each other very closely. However, the thymol turbidity test usually showed a very slight elevation after the cephalin flocculation reaction had become negative.

Occasional patients with chronic hepatitis following acute infectious hepatitis showed definite differences in the behavior of the two tests. One patient who had marked symptoms of fatigue and liver tenderness always showed a negative cephalin flocculation reaction and a positive thymol turbidity reaction of more than 12 units in twenty-five simultaneous determinations over a period of one year. The reverse was also found in an occasional case but in general the thymol turbidity reaction was the more useful test in following the prolonged course of chronic hepatitis. (Table III.)

In cirrhosis of the liver the two tests also paralleled each other closely. Thirteen per cent of the alcoholic group of cirrhosis patients showed consistently negative cephalin flocculation reactions, as compared with 17 per cent for the thymol turbidity test. It is of significance that negative reactions for these two tests were usually found in the same patients although serum protein abnormalities were present. In general, the cephalin flocculation reaction was more definitely positive in the group of cirrhosis patients who showed only slight elevation of the thymol turbidity test values.

COMMENTS

The finding that 100 per cent of the patients with infectious hepatitis showed a higher maximal result for the thymol turbidity test than the highest value found in a normal control group demonstrates the value of this reaction for diagnosis of acute

liver damage. Its chief disadvantage, however, is that the intensity of the reaction is not an index to the severity of the liver damage. This was also found to be true in patients with cirrhosis of the liver in whom the test proved to be of little value. The reaction is certainly not an estimate of the degree of aberration of liver function and should not be termed a liver function test. It is instead a sensitive indicator of acute liver damage. The degree of elevation in serum lipids and in the globulin fractions, which are the major components of the serum effecting a positive reaction, can hardly be considered indices of the degree of aberration of liver function. These components exhibit a delayed rise following acute liver damage, the exact significance of which is not clearly understood. It seems possible that these changes are related to the process of healing and regeneration of liver tissue and are therefore an indirect indication of acute damage.

The marked difference in values for the thymol turbidity test in alcoholic and non-alcoholic patients with cirrhosis of the liver is of some interest because it suggests a difference in the mechanism of causation of the cirrhosis. A majority of the patients in the non-alcoholic group showed marked hypergammaglobulinemia. The greater intensity of the thymol turbidity reaction in the non-alcoholic group of patients with cirrhosis reflected the more pronounced aberrations in gamma globulin in that group.

Some of the highest values for the thymol turbidity test were found in sera from patients with kala-azar in which there was extreme elevation of the gamma globulin fraction. Sera from patients with other parasitic diseases demonstrated an elevation of the thymol test which closely paralleled the elevation of total globulin. In these conditions there is evidence that the liver is involved. In malaria, for example, mild non-hemolytic jaundice is sometimes present and other liver function tests that do not depend on the globulin aberrations are positive.¹³ The liver lesion in kala-azar is

characterized by marked infiltration of inflammatory cells. Patients with unusual cirrhosis of the liver exhibiting extremely high gamma globulin and thymol turbidity values also showed a very marked cellular infiltration in the liver. The cellular reaction in the livers of patients with infectious hepatitis has often been described. In direct contrast, the hypergammaglobulinemia of multiple myeloma was not associated with a positive thymol turbidity reaction. Patients with cirrhosis of the liver following chronic alcoholism often showed elevation of the gamma globulin fraction in the presence of a negative thymol turbidity reaction. This was also true of patients with fatty livers. It was in the patients who exhibited a hyperglobulinemia associated with cellular infiltration of the liver that the thymol test correlated with the elevation in gamma globulin. These observations demonstrate that the test has some specificity and elevated values appear to be associated with those conditions in which an inflammatory process is present in the liver.

SUMMARY

In a group of seventy-six patients with infectious hepatitis who were followed throughout their illness the thymol turbidity test in every case showed a maximal value that was higher than the highest value obtained in a control group of forty-six patients. The results would appear to demonstrate the value of this reaction for the diagnosis of acute liver damage.

No correlation between severity of symptoms and degree of aberration in the thymol turbidity test could be found. The test proved to be of particular use in evaluating persistent symptoms following infectious hepatitis.

Patients with cirrhosis of the liver associated with chronic alcoholism showed considerably lower values for the thymol turbidity test than did patients in a non-alcoholic group. The test was of little value in estimating the degree of involvement of the liver in patients with cirrhosis.

Markedly positive reactions were associ-

ated with hyperglobulinemia in various parasitic diseases and other conditions in which an inflammatory process in the liver was present.

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Liver Function Tests in the Differential Diagnosis of Jaundice*

T. L. ALTHAUSEN, M.D.

San Francisco, California

IN a paper read before the 1946 Annual Meeting of the American Medical Association the author discussed the clinical diagnosis of jaundice with special attention to the value of data obtained from the history and physical examination of 100

TABLE I

DISTRIBUTION OF CASES ACCORDING TO TYPES OF JAUNDICE

<i>Obstructive Jaundice</i>	
Common duct stone.....	39
Carcinoma of the pancreas.....	44
Lymphosarcoma.....	1
Stricture of the common duct.....	2
	86
<i>Parenchymatous Jaundice</i>	
Portal cirrhosis.....	42
Biliary cirrhosis.....	3
Xanthomatous biliary cirrhosis.....	1
Acute hepatitis.....	47
Drug toxicity.....	5
Acute yellow atrophy of the liver.....	3
Primary carcinoma of the liver.....	1
	102
<i>Hemolytic Jaundice</i>	
Congenital hemolytic icterus.....	2
Total	190

patients.¹ The present paper is devoted to a discussion of the value of various laboratory tests in the differential diagnosis of jaundice and contains an analysis of 190 cases in which the diagnosis was definitely established by operation, autopsy or clinical course. (Table I.)

The conventional classification of jaundice into "hemolytic," "obstructive," and "parenchymatous" types according to the original cause of jaundice is followed in this paper.² The importance of making a differential diagnosis at least as to the type of

jaundice present in a given patient lies in the fact that in cases of obstructive jaundice surgical operation for removal of the obstruction or for a palliative anastomosis of the gallbladder to the duodenum is the only effective treatment, whereas in cases of parenchymatous jaundice surgical treatment is useless and contraindicated.

In this discussion the emphasis is placed on the differentiation between obstructive and parenchymatous jaundice. Hemolytic jaundice is uncommon and patients suffering from chronic hemolytic icterus are not very ill so that operation on the biliary passages is rarely considered. In addition there are several laboratory findings which, in the aggregate, are characteristic of hemolytic jaundice. These findings are: An icteric index under 50 units, a normal amount of bile pigment in the stools, absence of bilirubin with the presence of large amounts of urobilinogen in the urine, "indirect" reaction with the qualitative Van den Bergh test, and an increased reticulocyte count in the blood.

Liver function tests can be divided into two classes. In the first class belong the so-called "excretory" tests in which a patent biliary system is necessary for the normal outcome of the test. An example of this class is the Rose Bengal dye excretion test. In the second class belong the so-called "metabolic" tests which are independent of the state of the bile passages. An example of this class is the galactose tolerance test.

* From the Division of Medicine, University of California Medical School, San Francisco, California. Read before the First Mexican Congress of Medicine, Mexico City, August 4-10, 1946.

In the differential diagnosis of jaundice we can rule out at once the use of all excretory liver function tests except the qualitative Van den Bergh test. The presence of jaundice indicates that the ability of the liver to excrete bilirubin is impaired and for this reason we cannot expect normal excretion of other substances such as dyes—used to estimate hepatic function—which must leave by way of the bile. Moreover, the fact that the liver is unable to excrete normally various substances is of no help in differential diagnosis because this may be due either to an extrahepatic block of the common bile duct or to pathologic changes in the hepatic cells.

The qualitative Van den Bergh test distinguishes between “indirect” bilirubin which enters the blood from the reticulo-endothelial cells and “direct” bilirubin which enters the blood with the bile, having previously been excreted by the liver. In hemolytic jaundice which is caused by excessive hemolysis and overproduction of “indirect” bilirubin this test is of value because in most cases it gives the “indirect” reaction for many weeks after onset of jaundice. During the early stage of parenchymatous jaundice cloudy swelling of the hepatic cells diminishes the ability of the liver to take up “indirect” bilirubin which then accumulates in the blood. Later necrosis of some of the cells of the liver takes place leaving openings in the walls of the bile capillaries through which bile begins to enter the blood bringing with it “direct” bilirubin. Accordingly in the early stage of parenchymatous jaundice the Van den Bergh test gives the “indirect” reaction whereas later a mixed or “biphasic” reaction is the rule. In obstructive jaundice bile with “direct” bilirubin enters the blood from the first. Later as the back pressure of bile begins to injure the hepatic cells they are no longer able to take up normal amounts of “indirect” bilirubin and the

latter also accumulates in the blood. Accordingly in obstructive jaundice the Van den Bergh test at first gives the “direct” reaction but later this is also changed to the “biphasic” type. For this reason the qualitative Van den Bergh test is useful for the differential diagnosis of jaundice only during the first week of jaundice, except in cases of hemolytic jaundice.

The principle underlying the use of metabolic liver function tests in the differential diagnosis of jaundice is that in obstruction of the common bile duct the hepatic parenchyma is usually intact whereas in various forms of acute or chronic hepatitis there are diffuse pathologic lesions in the hepatic cells resulting in more or less widespread necrosis. On the basis of this principle, in an ideal case we should with the use of any metabolic test get normal hepatic function in obstructive jaundice and impaired hepatic function in parenchymatous jaundice. However, these ideal conditions prevail only during the first few days after the onset of jaundice. Unfortunately, several days usually elapse before the patient or his family notice the yellow color of the sclerae and skin and then more time is lost because, unless pain is also present, jaundice apparently does not alarm most patients who often wait for weeks and sometimes months before seeking medical advice. As a result the back pressure of bile in obstructive jaundice causes damage to the hepatic cells and a week or at the most ten days after the obstruction becomes established most metabolic tests begin to register diminished function. In this way the usefulness of most of the metabolic liver function tests for the differential diagnosis of jaundice is lost soon after the onset of jaundice. Among the otherwise useful tests which in my experience are of little value for this purpose are the hippuric acid test, the cephalin flocculation test, determinations of total cholesterol, of alkaline phosphatase and of

urobilinogen in the urine according to the method of Wallace and Diamond.³

Fortunately there are two metabolic tests of liver function which enable the physician to distinguish between obstructive and parenchymatous jaundice in a large majority of cases. These tests are the intravenous galactose tolerance test and the response of prothrombin to vitamin K.

1. *The Intravenous Galactose Test.* The value of galactose in the differential diagnosis of jaundice lies in the observation that unlike most other functions of the liver the ability to metabolize galactose is impaired very little by obstructive jaundice of even several months' duration. In a previous paper⁴ we called attention to the unreliable results obtained with the conventional oral galactose test which, in addition to the ability of the liver to metabolize galactose, is influenced by the rates of intestinal absorption and renal excretion of this sugar. At the same time the following method for doing the test was described:

After an oxalated blood sample has been obtained, a dose consisting of 1 cc. of a 50 per cent solution of galactose per kilogram of body weight is injected intravenously over a period of four to five minutes with a 100 cc. syringe with excentric tip, fitted with a short No. 19 gauge needle. Another oxalated blood sample is secured seventy-five minutes after the injection. Glucose is removed from the blood samples by fermentation with yeast according to Raymond and Blanco's⁵ modification of Somogyi's method. The filtrates are analyzed for the non-fermentable reducing substance by the Hagedorn-Jensen method. In order to obtain the galactose content of the blood, the figure for reducing substances in the fasting blood is subtracted from the corresponding figure in the seventy-five-minute specimen. A correction of 24 per cent must be added if conversion tables for glucose are used. The details of the procedure and its adap-

tation to the Folin-Wu method have been described elsewhere.⁶ The test is usually performed on the fasting patient, but in our experience such food as toast and coffee has produced no rise in the galactose level of the blood.

With this method almost all patients with obstructive jaundice of less than six months' duration had less than 20 mg. per cent of galactose in the blood seventy-five minutes after the injection of galactose while a large majority of patients with parenchymatous jaundice had more than 20 mg. of galactose in the blood.

In the present series all except one patient with uncomplicated obstructive jaundice due to stone in the common bile duct had less than 20 mg. per cent of galactose in the blood at the end of the test. In the one exception the blood galactose was 28 mg. per cent. Eight patients with cholelithiasis and superimposed biliary cirrhosis had higher galactose values. All of the latter patients had a long history of repeated attacks of biliary colic associated with jaundice, chills and fever, so that it was easy to distinguish this group clinically from patients with uncomplicated obstructive jaundice. In all of these patients the clinical diagnosis of biliary cirrhosis was confirmed by operation and in half of them in addition by biopsy of the liver.

In all but three patients with uncomplicated obstructive jaundice due to carcinoma of the pancreas the blood galactose was under 20 mg. per cent. In the three exceptions the blood galactose was under 30 mg. per cent. Three patients with carcinoma of the pancreas had considerably higher values for galactose. Two of them also had cirrhosis of the liver as shown by operation and biopsy, and the third patient had massive metastatic growths in the liver. Two patients with jaundice due to benign post-operative stricture of the common duct had a normal galactose tolerance. Seven pa-

tients had obstructive jaundice from various causes longer than six months and in four of them considerable impairment of galactose tolerance was found.

In summary (Table II), practically all (95 per cent) patients with uncomplicated

such as ascites, "spider" angiomas and subcutaneous collateral circulation made the diagnosis clear.

Seventy-seven per cent of patients with acute hepatitis had a galactose blood level in excess of 20 mg. per cent. Twenty-three

TABLE II

THE RESULTS OF THE INTRAVENOUS GALACTOSE TEST AND OF THE PROTHROMBIN RESPONSE TO VITAMIN K IN 188 PATIENTS WITH OBSTRUCTIVE OR PARENCHYMATOUS JAUNDICE

Type of Jaundice	No. of Cases	I.V. Galactose Test		Prothrombin Response to Vitamin K	
		Under 20 mg. (per cent)	Over 20 mg. (per cent)	Positive (per cent)	Negative (per cent)
Obstructive Jaundice { All cases*	86	82	18	91	9
	Uncomplicated cases	68	95		
Parenchymatous { All cases†	102	24	76	4	96
	Jaundice { Cases with icteric index over 50 units . . .	80	4		

* Including cases with biliary cirrhosis.

† Including cases with jaundice which was slight (icteric index under 50 units) or of short duration.

obstructive jaundice were diagnosed correctly by the intravenous galactose test. If we are to include in the group of obstructive jaundice the cases complicated by hepatic cirrhosis and the case with massive metastases to the liver, we still get a correct answer in 82 per cent of the cases. The mean galactose blood level of all patients with obstructive jaundice was 14 mg. per cent.

Seventy-six per cent of patients with cirrhosis of the liver had more than 20 mg. per cent of galactose in the blood. All but one of these patients had an icteric index over 50 units. Twenty-four per cent of patients with cirrhosis of the liver had less than 20 mg. per cent of galactose in the blood and all of them had an icteric index under 50 units. In addition to the mild degree of icterus which usually robs the case of urgency because surgical intervention is not contemplated, in most of the latter cases the presence of other signs pointing to parenchymatous hepatic disease

per cent had less than 20 mg. per cent of galactose in the blood. In the latter group, in all but three cases the hepatitis was mild (with an icteric index under 50 units) or of short duration and undergoing rapid improvement at the time the test was performed.

Three patients with acute yellow atrophy of the liver had a striking inability to metabolize galactose. Their blood galactose levels were 129, 139 and 145 mg. per cent. The highest figure for galactose in the blood observed by us in acute hepatitis with recovery was 116 mg. per cent and the highest figure obtained in cirrhosis of the liver was 92 mg. per cent. This limited experience suggests that galactose levels over 125 mg. per cent are of grave prognostic significance. This finding is of all the more value since in two of the three cases extremely high values for galactose were obtained by us before other indications of the gravity of the situation appeared and while the patients had

few subjective complaints. In one of these cases the outcome of the test was instrumental in bringing a close relative from a distant part of the country to the patient's bedside before death occurred.

Five patients with slight jaundice caused by toxic action of drugs (two cases due to cinchophen, two due to sulfonamides and one due to arsphenamine) were studied with the intravenous galactose test. Two of these patients had a galactose blood level of more than 20 mg. and three had a level of less than 20 mg. These results suggest that the galactose test is unreliable in the diagnosis of jaundice induced by drugs. However, this is not very important since a history of preceding medication with one of the hepatotoxic drugs is relatively easy to obtain.

In summary (Table II), 76 per cent of all patients with parenchymatous jaundice were identified correctly by means of the intravenous galactose test. Were we to exclude from our material patients with mild jaundice (with an icteric index under 50 units) or with jaundice lasting less than a week, the accuracy of the test in parenchymatous jaundice would rise to 96 per cent. The mean galactose level of the blood of all patients with parenchymatous jaundice was 56 mg. per cent. King and Aitken⁷ as well as MacLagan⁸ obtained comparable results with the intravenous galactose test. Combining the results of the intravenous galactose test in all cases of jaundice, it is seen that the outcome of the test alone made the differentiation between obstructive and parenchymatous jaundice in our series in three out of four cases. When certain simple additional clinical data are taken into consideration, it becomes possible to determine correctly the type of jaundice in almost all cases.

2. *Prothrombin Response to Vitamin K.* Maintenance of a normal prothrombin level in the plasma is one of the functions of the liver. This function can be fulfilled

only in the presence of an adequate supply of vitamin K from the intestine. Obstructive jaundice lowers the prothrombin level by interfering with intestinal absorption of vitamin K and creating a vitamin K deficiency. Such a deficiency hypoprothrombinemia is corrected rapidly (often in six hours) by parenteral administration of vitamin K. Parenchymatous jaundice produces hypoprothrombinemia by interfering with the ability of the liver to form prothrombin. Consequently in the latter case administration of vitamin K either does not raise the prothrombin level at all or does so only slowly, and then the prothrombin level often decreases again in spite of continued administration of vitamin K. This difference, as has been repeatedly pointed out,⁹⁻¹³ can be used for the differential diagnosis between obstructive and parenchymatous jaundice.

In the present study the prothrombin level was determined by the method of Quick.¹⁴ The patient was then given an injection of 1 mg. of vitamin K* and the prothrombin determined again twenty-four to forty-eight hours later. Elevation of the prothrombin level was considered significant only if the original level was 70 per cent or less and the increase 20 per cent or more.

Among our patients with obstructive jaundice, 91 per cent responded with a significant increase of an initially low prothrombin concentration. Among those failing to respond, superimposed biliary cirrhosis, the presence of which was easy to determine from the history, accounted for one-half of the cases. Allen¹⁵ also found that the presence of cholangitis with fever impaired the prothrombin response. In the group of our patients with parenchymatous jaundice, 96 per cent showed no increase in the prothrombin level. These figures indi-

* "Hykinone" ampules by Abbott Co. were used in this work but any other preparation of vitamin K suitable for parenteral administration can be employed.

cate a very satisfactory accuracy on the part of the prothrombin response to vitamin K in the differentiation of obstructive from parenchymatous types of jaundice. There was also excellent correlation between the results of the intravenous galactose test and the response of a low prothrombin level to vitamin K.

COMMENTS

In the diagnosis of diseases of the liver in general and in the differential diagnosis of jaundice in particular, liver function tests are an important diagnostic aid but they do not take the place of a good history or a careful physical examination. In many patients with jaundice the correct diagnosis can be made from the history and physical examination alone. In an additional number of cases ordinary laboratory studies and roentgenologic examinations will answer the question whether the jaundice is due to extrahepatic block and surgical intervention is necessary, or whether it is due to parenchymatous disease of the liver and medical treatment alone is indicated. Ordinary laboratory studies are particularly helpful in ruling out hemolytic jaundice. However, in most cases final recourse is made to liver function tests. It must be remembered that excretory liver function tests are useless in patients with jaundice. Among metabolic functions of the liver most decisive for the differentiation between obstructive and parenchymatous jaundice, in my experience, is the ability of the liver to metabolize galactose and to produce prothrombin following an injection of vitamin K. If these functions of the liver are not impaired or are impaired only slightly, the case is in the domain of the surgeon. If they are markedly impaired, the case is almost always strictly a medical problem. Although the results of either the intravenous galactose test or of the prothrombin response to vitamin K, especially if taken in conjunction

with the history and physical findings, possess a high degree of accuracy for the differential diagnosis, it is advisable, whenever possible, to do both tests in every patient with jaundice.

Technically the galactose test is simple and after a little practice with galactose solutions of known concentration can be performed in any laboratory which is equipped to do blood sugar determinations. On the other hand, accurate prothrombin determinations are fairly difficult and reliable results usually require a larger laboratory where workers experienced in prothrombin determinations perform the tests.

SUMMARY

1. The pathologic physiology of different types of jaundice and its relation to "excretory" and "metabolic" liver function tests is discussed.

2. The results of the intravenous galactose test and of the response of prothrombin to vitamin K in the differential diagnosis of 190 patients with jaundice are analyzed.

3. The importance of distinguishing between obstructive jaundice for which surgical operation is the only effective treatment and parenchymatous jaundice which constitutes a strictly medical problem is pointed out.

4. The usefulness of the intravenous galactose test is demonstrated by the fact that, when taken alone, it made possible the differentiation between obstructive and parenchymatous jaundice in three out of four cases. When taken in conjunction with certain simple additional clinical data, this test allowed the identification of the type of jaundice in almost all cases.

5. The diagnostic accuracy of the prothrombin response to vitamin K is shown by the fact that it was present in nine of ten patients with obstructive jaundice and was absent in the same proportion of patients with parenchymatous jaundice.

CONCLUSIONS

1. Appropriate liver function tests are an important aid in the differential diagnosis of jaundice when taken in conjunction with data from the history, physical findings and ordinary laboratory studies.

2. With the help of the intravenous galactose test and the response of prothrombin to vitamin K it is possible to arrive at a correct diagnosis as to the type of jaundice in over 90 per cent of cases.

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Minimal Yet Adequate Program of Liver Function Studies in the Differential Diagnosis of Jaundice*

HARRY SHAY, M.D. and H. SIPLET

Philadelphia, Pennsylvania

THE problem of the differential diagnosis of jaundice, considered on the basis of the simplest possible classification (hemolytic, hepatocellular or obstructive), offers little difficulty with respect to identification of the first group, hemolytic jaundice. The enlarged spleen, reticulocytosis, spherocytosis and increased fragility of the red blood cells, the increased urobilinogenuria and hyperbilirubinemia to concentrations above that of the kidney threshold but with no bilirubin appearing in the urine, provide ample data for the diagnosis of congenital or acquired hemolytic icterus. Hepatocellular and obstructive jaundice present somewhat different problems. Although clinical differentiation between these two types of jaundice can frequently be made, it is often impossible to do so despite a carefully taken history and exhaustive physical examination. The age of the patient, pain, itching, the tint of the skin, weight loss and palpable spleen are signs and symptoms of statistical interest and value, but experience has shown that they often cannot be relied upon in making the differential diagnosis in the individual case. All too frequently patients with severe acute liver damage are subjected to the additional trauma of anesthesia and operation in an attempt to rule out extrahepatic obstruction. The hazards of undue delay in operation in cases of obstructive jaundice are well known.

The literature is replete with studies of liver function tests in jaundice, tests whose avowed purpose is to overcome these diagnostic uncertainties. Too often such studies concern themselves more with the establishment of the superiority of one test over another than with the development of a minimum yet adequate liver function study that will make possible differentiation between the two types of jaundice. The multiple functions of the liver and the known "dissociation" of the effects of hepatic damage upon these functions preclude the development of a single test that will serve such a purpose. Although the number of liver function tests that has been devised is legion and is constantly increasing, practicality dictates that only a few tests be used in any one study. In our experience we have found that a minimum yet adequate program can be developed if certain criteria are kept in mind. In addition to a reliable method for measuring the degree of icterus, such a program should include at least two tests which give positive results in obstructive jaundice and two whose results are positive in hepatocellular jaundice. The tests selected should evaluate different functions of the liver. By so doing, limitations imposed by the "dissociation" of effects of hepatic damage may be obviated.

In view of the dynamic character of liver function, especially in hepatocellular jaundice, tests for liver function should be per-

* From the Fels Research Institute, Temple University, Philadelphia, Pennsylvania.

formed as soon as jaundice is detected. Furthermore, because of the changing functional picture a real appreciation of what is occurring in the liver can be obtained only by repeating the tests at short intervals (preferably three or four days). To criticize the value of a test upon the basis of a single determination in a jaundiced patient betrays a lack of understanding of liver physiology. Thus, the variable intensity and duration of obstructive features in hepatocellular jaundice may give apparently misleading results in a single examination with a test which is affected primarily by obstruction in the biliary passages. Similarly, delay in applying the tests in the course of obstructive jaundice may result in the superposition of hepatocellular damage, producing what superficially appear to be false results in tests dependent upon hepatic cell damage. An appreciation of the mechanisms involved in the tests used, a proper combination of tests and their early and repeated use in jaundice usually give a feeling of assurance in the differential diagnosis of hepatocellular and obstructive jaundice which cannot be obtained by clinical observation alone. Moreover, the tests so used enable the clinician to follow the changing functional activity of the liver and permit an earlier and sounder prognosis.

Tests to Measure Intensity of Jaundice. Table 1 includes the liver function tests which we have found most useful in the study of jaundice. As a measure of the intensity of jaundice we found the quantitative van den Bergh test preferable to the icterus index. Since the color produced in the van den Bergh test results from a chemical reaction between bilirubin and Ehrlich's diazo reagent, errors can be avoided which may occur in the simple color matching of serum with the potassium dichromate standard used in determining the icterus index.

When laboratory facilities are very limited, the methylene blue test for "bilirubin"

in the urine may serve as a useful although less accurate indicator of the course of icterus. This test was first described by Franke in 1931. He recommended that it be performed by the dropwise addition of a 0.2 per cent solution of methylene blue to

TABLE 1
TESTS RECOMMENDED FOR THE DIFFERENTIAL DIAGNOSIS OF
OBSTRUCTIVE AND HEPATOCELLULAR JAUNDICE

1. Measurement of the Intensity of Jaundice
 - a. Quantitative van den Bergh
 - b. Icterus index
 - c. Methylene blue test (urine)
2. Tests Affected Primarily by Hepatic Cell Damage; Function Tested
 - a. Galactose tolerance test—carbohydrate metabolism
 - b. Serum cholesterol esters (ester ratio)—lipid metabolism
 - c. Cephalin cholesterol flocculation test—protein metabolism
 - d. Colloidal gold test—protein metabolism
 - e. Thymol turbidity test—protein metabolism
3. Tests Affected Primarily by Obstruction in the Biliary Passages
 - a. Serum total cholesterol
 - b. Serum phosphatase (alkaline)

5 cc. of urine. According to Franke,¹ in the presence of bilirubin the urine turns intensely green with the addition of the first drop of methylene blue. With additional methylene blue the specimen will become green, blue green and finally blue. The amount of methylene blue required to produce these color changes he believes is proportional to the quantity of bilirubin in the urine.

Myers² studied this test in employees who developed liver damage while working with tetrachlorethane. He found that the test became positive before the serum bilirubin concentration was elevated. As the jaundice disappeared the methylene blue test gave normal results when the serum bilirubin concentration was still above the kidney threshold level. In a recent issue of the *Journal of the American Medical Association*, Gellis and Stokes³ found the test useful in evaluating the course of infectious hepatitis. They recommend the addition of two drops of a 0.2 per cent aqueous solution of methylene blue to 5 cc. of a pre-breakfast

urine specimen. If a green color results, more methylene blue is added dropwise and the last drop required to convert the green color to blue is recorded. Pipettes are used which deliver twenty drops of the solution per cc. (0.05 cc./drop). When readings are made by natural light, no difficulty is found in determining the change from green to blue. In a letter to the editor of the same issue of the Journal, Gellis, Neefe, Reinhold and Stokes⁴ determine the final reading as one drop less than the number needed to produce the final color change. They regard the test as positive for bilirubin when more than four drops must be added. If more than five drops are required, the urine is diluted with distilled water and methylene blue is again added drop by drop until the end point is reached. Correction is made for the dilution factor. Dilution of the urine avoids difficulty in reading the end point. In accord with the results reported by Myers² in liver damage due to tetrachlorethane, Gellis and Stokes³ found that the test may be positive in infectious hepatitis in the preicteric stage and negative in the recovery period when the icterus index is still elevated. They³ believe the test can be of service in evaluating the course of the disease and in the prediction of impending relapse. The data in Figure 1, illustrating a case of infectious hepatitis with incomplete recovery and recrudescence, are in agreement with this view. (Fig. 1.)

The mechanism responsible for the color changes produced by the addition of methylene blue solution is not clear at present. Franke¹ believes it to be a specific reaction between methylene blue and bilirubin and that two drops of the methylene blue solution are equivalent to 0.1 mg. of bilirubin. Myers² does not share this opinion and attributes the green color in the reaction primarily to a mixture of the yellow and blue pigments. Reinhold⁵ is in agreement with this, although he thinks that some

chemical reaction occurs between methylene blue and bilirubin. Stokes, Gambill and Osterberg⁶ conclude from spectrophotometric studies of methylene blue, sodium bilirubinate and their mixtures that the color reaction of the mixtures is dependent upon a blending of colors. Their conclusion is based upon the fact that the green solution of the mixtures gave two absorption bands, one of sodium bilirubinate and one of methylene blue, without producing any new band.

Gellis and Stokes³ tested the pre-breakfast urine in 1000 patients with diseases other than hepatitis. In 74 per cent of the specimens, two drops of methylene blue solution produced a blue color, in 24.3 per cent, three drops and in 1.7 per cent, four drops were required. We have recently tested the pre-breakfast urine in 100 patients with functional and organic gastrointestinal disease other than liver disease. The final reading in fifty-six specimens was one drop, in thirty-five, two drops, three drops in eight and four drops in one.

Recording quantitative results in drops is frowned upon in many quarters. The variation in size of drops deliverable from a 1 cc. pipette, coupled with the effort necessary for the control of dropwise delivery, prompted us to use a 5 cc. burette set up for permanent use. When not in use, evaporation from the burette is prevented by a rubber stopper. The burette is graduated in 0.2 cc. units and is fitted with a micro dropper which permits fractionation of the drops. Normal urine (5 cc.) would, therefore, require 0.2 cc. or less of the methylene blue solution for production of a blue color. This modification in procedure may eliminate considerable error with urines of high "bilirubin" content that require considerable dilution.

Tests Affected Primarily by Hepatic Cell Damage. Of the tests designed to investigate the carbohydrate metabolism of the liver, the

galactose tolerance test alone has survived. Introduced by Bauer⁷ in 1906, it came into general use in this country when one of us⁸ showed its reliability if applied only to the differential diagnosis of obstructive and hepatocellular jaundice. It still remains one

will be recovered in the urine in the ensuing five hours. The same results are obtained in cases of uncomplicated obstructive jaundice. In hepatocellular jaundice more than 3 Gm. are usually excreted in the five-hour period. Effective use of the galactose toler-

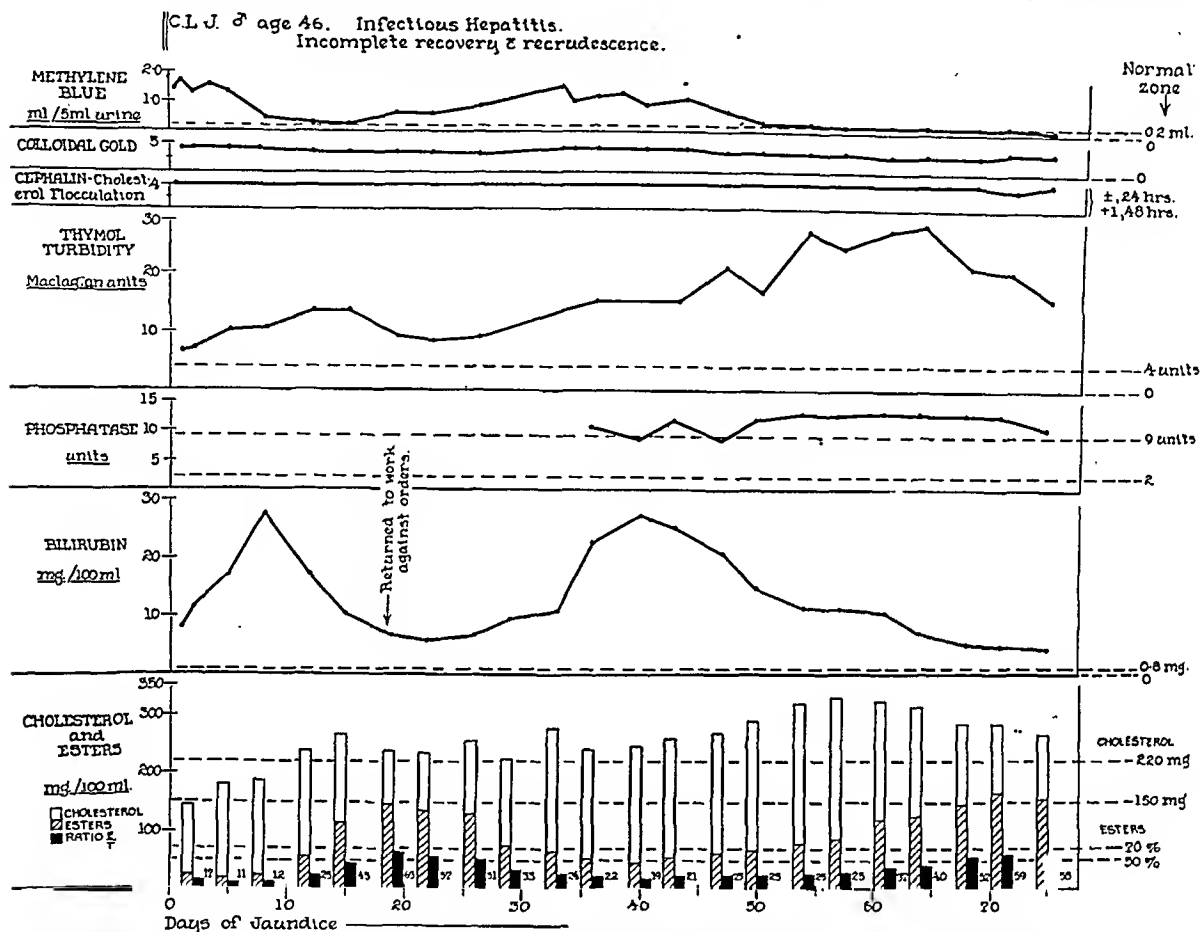


FIG. 1. Methylene blue test. Note return to normal base line in initial attack (seventeenth day) and in recovery following recrudescence (fiftieth day) while serum bilirubin levels were still well above the kidney threshold. The rise above values was the first indication of recrudescence of the disease and in this case this test was a more sensitive index of the change than was the drop in cholesterol ester ratio. It would be of interest to compare these two tests on the same days in very early cases or in pre-icteric stage of experimentally induced hepatitis. The rise of the cholesterol ester ratio to 63 per cent on the twentieth day, followed by the drop to 57 per cent on the twenty-third day and to 51 per cent on the twenty-seventh day we considered evidence of impending recrudescence even though no appreciable change in the serum bilirubin level had as yet occurred. The usual behavior of the cholesterol ester ratio in recovery from infectious hepatitis is shown in Figure 2 after the thirty-second day by the maintenance of the ratio near the upper limits of normal for some time into the recovery period. Recovery after recrudescence was slow and flocculation tests all remained abnormal after the cholesterol partition had returned to normal.

of the most useful tests for that purpose, especially when laboratory facilities are limited. In principle, the test is based upon the specific utilization of galactose by the liver. Under a test load of 40 Gm. of galactose administered orally to a normal individual after an overnight fast, 3 Gm. or less

ance test, or any liver function test in which positive results are dependent upon acute diffuse parenchymal damage, can be made only if there is constant awareness of the dynamic state of liver function, as previously stated. (Fig. 2.)

Cholesterol Partition. Serum cholesterol

partition and alkaline serum phosphatase have been discussed so fully in the literature that we shall limit ourselves to a consideration of a few essential details.⁹ In normal blood serum, esterified cholesterol makes up 50 to 70 per cent of the total cholesterol. In

impaired. This results in a lowering of the percentage of cholesterol esters in the blood, often to very low levels.

Since an appreciable increase in total cholesterol in jaundice is dependent upon biliary tract obstruction, and a low ester

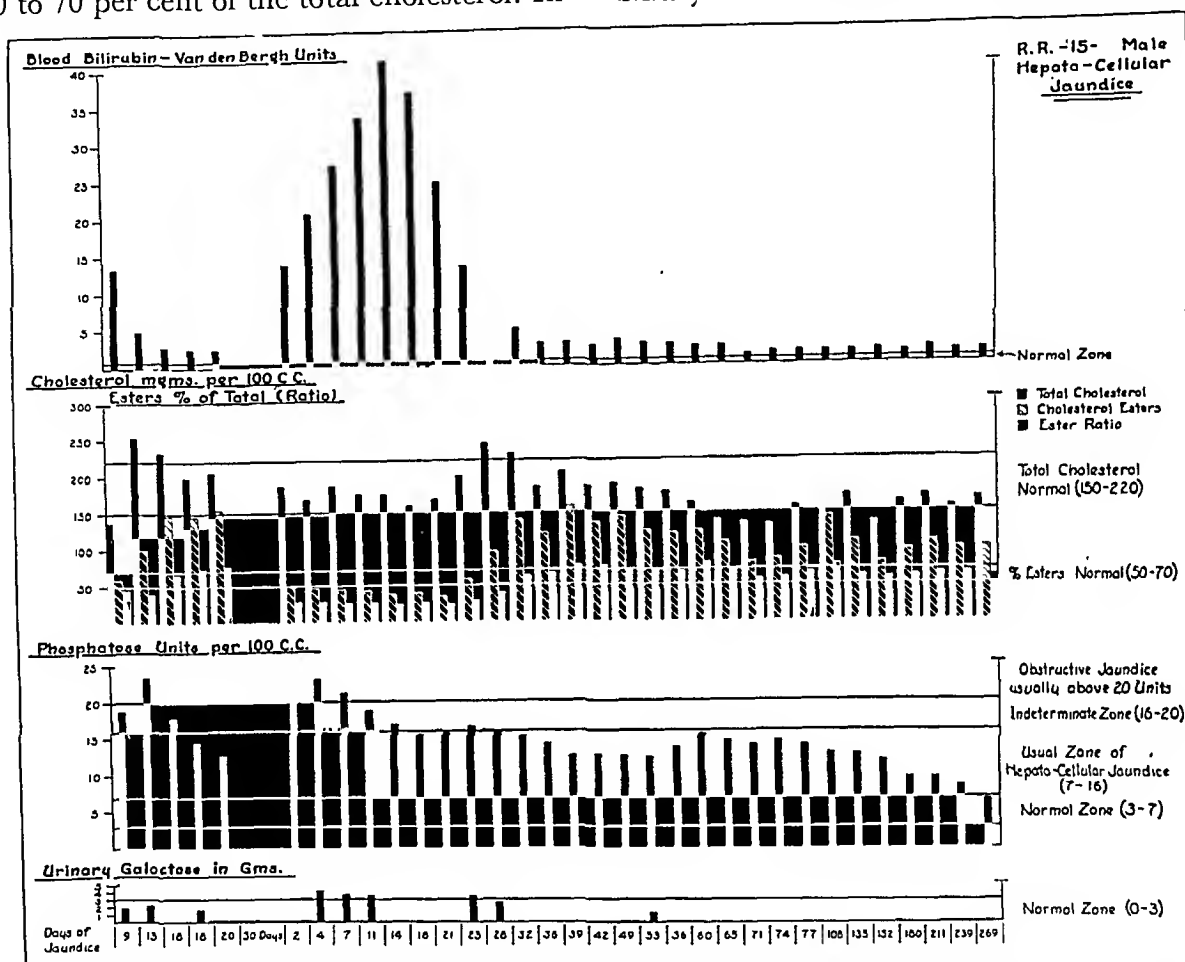


FIG. 2. Infectious hepatitis with recurrence. The levels of serum phosphatase reaching the obstructive zone are in this instance probably due to the higher values of phosphatase normally possible at this age level. The results with the galactose tolerance show the need for functional studies early in jaundice. In the first attack the disease was apparently very mild and the patient already in the recovery period when he entered the hospital on the ninth day of jaundice. Although the cholesterol ester ratio had not yet returned to normal, carbohydrate metabolism in the liver had recovered. In the recurrence, however, the galactose tolerance test was positive on the fourth day and remained so until the twenty-fifth day, but again returned to normal before the cholesterol ester ratio. This relationship of recovery is not always maintained. The need for application of liver function tests early in jaundice is obvious.

obstructive jaundice there is usually a rise in total serum cholesterol. Esterification, however, keeps pace with this change, so that the percentage of cholesterol esters remains within the normal range. In hepatocellular jaundice there is generally no striking change in the total cholesterol concentration and esterification in the liver is

ratio is dependent upon acute diffuse hepatic cell damage, the cholesterol partition supplies two tests—one gives a positive result in obstructive and the other in hepatocellular jaundice. It is not only a very reliable procedure for the differential diagnosis of these two types of jaundice but when determined frequently during the course of

the disease it is also a dependable prognostic index in hepatocellular jaundice. The usual picture in recovery from this type of jaundice will show a moderate increase in total cholesterol and the percentage of esters will often hug the upper limits of normal. Espe-

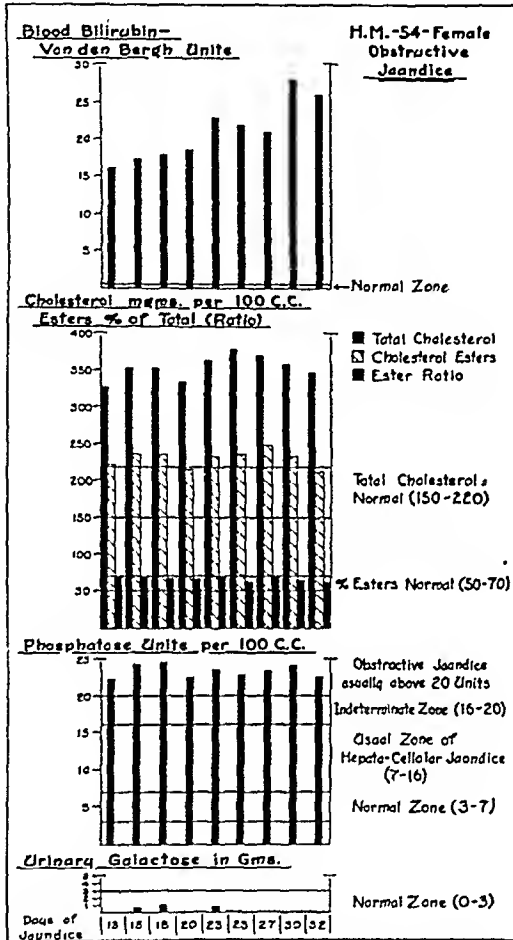


FIG. 3. Typical response of tests in a case of obstructive jaundice. Cause: carcinoma of head of pancreas.

cially significant is the fact that the esters will stay at a high normal level for some time. (Fig. 2, days 39 to 65.) Should the ester ratio consistently diminish shortly after normal values have been reached, recrudescence or recurrence of the disease may be suspected, even though the values for the ester ratio are still within normal limits. Figure 1 (days 20 to 30) illustrates this point. While making a very satisfactory recovery from an attack of infectious hepatitis, the patient decided, contrary to

orders, to return to work on the twentieth day of jaundice when his serum bilirubin was still 6 mg. On that day his cholesterol esters comprised 63 per cent of the total serum cholesterol. On the twenty-third day his cholesterol esters had dropped to 57 per cent and on the twenty-seventh day to 51 per cent. While these were not striking changes and the readings were still within the normal zone we were convinced that the patient was having a recrudescence in spite of the fact that from the twentieth day to the twenty-seventh day there were no clinical manifestations or increase of serum bilirubin to suggest such a change. The subsequent course of the disease justified that opinion. It is especially interesting to note that the methylene blue test which had returned to normal on the thirteenth day had again become abnormal on the sixteenth day.

Cephalin Cholesterol Flocculation. The flocculation tests are the most recent additions to the long list of liver function tests already in use in jaundice. The three tests in this group are (1) the Hanger cephalin cholesterol flocculation, (2) the colloidal gold and (3) the thymol turbidity tests. Of these the Hanger cephalin cholesterol flocculation is the oldest and has enjoyed the widest use. In 1938, Hanger¹⁰ described a simple test for recognizing disturbances in the hepatic parenchyma, noting the capacity of blood serum in these cases to flocculate a colloidal suspension of a cephalin cholesterol complex. A negative test is one in which no flocculation occurs. A plus four reaction is one in which there is complete flocculation. Varying degrees of precipitation are recorded as +, ++, or ++++. Flocculation is recorded at twenty-four and forty-eight hours and we consider as normal \pm flocculation at the former and +1 at the latter period. Hanger¹¹ found no significant flocculation in twenty-five cases of obstructive jaundice. In thirty-three of thirty-eight cases

of hepatitis and cirrhosis he obtained a prompt flocculation. In a number of these patients tested repeatedly during the course of the disease he observed a close correlation between the clinical severity of the hepatic disorder and the degree of flocculation.

Kabat et al.¹² showed the gamma globulin fraction to be the sole component of the serum to give a positive cephalin cholesterol flocculation test. The concept at first entertained that flocculation was due to an alteration in the gamma globulin fraction¹¹ was discarded when these investigators found no difference in the flocculating power of the gamma globulin fraction obtained electrophoretically from normal sera (negative reaction) and that obtained from hepatitis sera (strongly positive). It was evident that the failure of normal sera to cause flocculation of the cephalin cholesterol complex was due to the inhibiting action of some component of the serum other than the gamma globulin. Moore et al.,¹³ by the use of electrophoretically separated fractions of blood sera from normal people and from patients with hepatitis, found the flocculation-inhibiting action of the normal blood serum to be a function of the albumin fraction. On this basis, a positive flocculation could occur (1) if the gamma globulin fraction was increased, resulting in a relative decrease of albumin to a point insufficient to inhibit flocculation, (2) if a decrease in serum albumin occurs below the concentration at which it can inhibit flocculation, and (3) with a normal albumin level but a diminution in the flocculation-inhibiting power of the albumin fraction.

Colloidal Gold Test. Extensive studies on the mechanism of the colloidal gold reaction obtained with spinal fluid have related the type of reaction in pathologic conditions to variations in the balance between the precipitating activity of the globulin and the protective action of the albumin.¹⁴ There is evidence that change in the individual

globulin fractions, particularly in the euglobulin fraction, also plays an important rôle in the precipitation of colloidal gold.¹⁵ The fact that similar changes in plasma protein fractions are frequently observed in hepatic damage prompted Gray¹⁶ to apply the colloidal gold test to the study of liver disease. MacLagan¹⁷ recently greatly simplified the method by reducing the procedure to a single tube technic. By rigorously controlling the reaction of the medium with buffer solutions, he was also able to obtain greater specificity with the test and more readily reproducible results. The degree of positivity is dependent upon the precipitation of gold and the extent of decolorization of the supernatant. The result is recorded as plus five when precipitation of the gold is complete and the supernatant is water-clear. A plus one is a reaction in which a slight turbidity occurs. A++, +++, or++++ is recorded with increasing precipitation and decolorization of the supernatant. Readings are made at the end of twenty-four hours. With the simplified method, MacLagan saw no positive readings with sera from normal subjects. With Gray's method Mateer et al.¹⁸ reported a positive reaction in 10 per cent of the sera from normal subjects. MacLagan¹⁷ suggested the use of the test for the differentiation of obstructive jaundice and infectious hepatitis and reported only two positive results in thirty-four cases of obstructive jaundice and five negative readings in 105 cases of infectious hepatitis. In arsenical jaundice (twenty-one of thirty-five cases) and in Weil's disease (eight of seventeen cases) he¹⁷ found a much higher proportion of negative results than in infectious hepatitis.

Thymol Turbidity Test. In that delightful and charming little book, "The Way of an Investigator," which Cannon wrote shortly before he died, there is a chapter headed "Gains from Serendipity." The discovery and development of the thymol turbidity

test might be included as one of those gains. Serendipity, a word coined by Horace Walpole about the middle of the 18th century, had its origin in the title of an old fairy tale, "The Three Princes of Serendip" (former name of Ceylon), "the heroes of which were always making discoveries by accident and sagacity, of things they were not in quest of." In the discovery of the thymol turbidity test some accident but more sagacity was involved. Maclagan,¹⁹ seeking to prevent the development of molds in the barbitone buffer which he employed for the colloidal gold reaction, added a crystal of thymol to the buffer solution. When the thymol-treated buffer solution was added to certain sera the mixture became turbid or a precipitate developed. The sera in which these changes occurred were all obtained from cases of parenchymatous liver disease. From this chance observation Maclagan developed the thymol turbidity test. The test consists of a simple mixture of blood serum with a saturated solution of thymol in a barbitone buffer of pH 7.8. He measures the degree of turbidity by comparing the solution after one-half hour with the turbidity of the formazin standards devised by Kingsbury and his associates.²⁰ These standards have been used for many years in the rough quantitative determination of protein in the urine. Normal sera give readings of 0 to 4 units, the number of units being the number of milligrams of protein represented by the standard matched, divided by ten, multiplied by the dilution of the blood serum. Maclagan¹⁹ reported significantly positive values (above 4 units) in 120 of 130 cases of hepatitis and in only four of thirty-seven cases of obstructive jaundice. Watson and Rappaport²¹ point out that the easy preparation of stable test solutions containing weighted amounts of pure chemicals, the completion of the test in one-half hour instead of the forty-eight hours necessary for the Hanger test and a simple method of

measuring positivity, give the Maclagan test an advantage over the cephalin cholesterol flocculation.

Shank and Hoagland²² recently reported a modification of the thymol turbidity standard which permits turbidimetric measurement in the spectrophotometer. The turbidity of a given reaction is expressed in units derived from a standard absorption curve prepared with barium sulfate suspensions. We have found a close correlation of the readings obtained in the same sera with Shank and Hoagland's method and the Kingsbury standards, except when the readings are very low (less than 2 units). At these levels the electrophotometric reading is certainly more accurate than tube matching with the Kingsbury standards. Since the levels at which the discrepancies occur are all within normal limits, the lack of close correlation of the two methods at these levels is not of practical importance.

In his original paper Maclagan¹⁹ described the formation of a precipitate in positive tests when allowed to stand overnight. He apparently did not attach any special significance to these precipitates since he did not believe them to be an essential part of the reaction. In tests on seventy-six patients without demonstrable liver disease referred to later, we saw a precipitate in only one case on two occasions at eighteen hours with a reading of 2.5 and 2.8 units. This was in a severe iron deficiency anemia. We have, however, been impressed by the persistence of eighteen-hour precipitates for considerable periods after the half-hour readings have returned to normal in tests with sera from patients recovered from infectious hepatitis. We do not know the meaning of the persistent precipitate in the flocculation test at present. The continued production of some altered protein fraction or fractions of the blood serum after the other functions of the liver have been restored may be responsible. Such an

explanation appears plausible from the following studies on the disappearance of these precipitates in the reaction.

We attempted to quantitate the precipitate formed. To do so we read the turbidity photoelectrically one-half hour after the ad-

which the thymol turbidity reading returned to normal of 3.8 units on 5/9. Considerable precipitate had settled out at eighteen hours, since the turbidity of the supernatant was only 32 per cent of that of the half hour specimens. Table II shows the continued

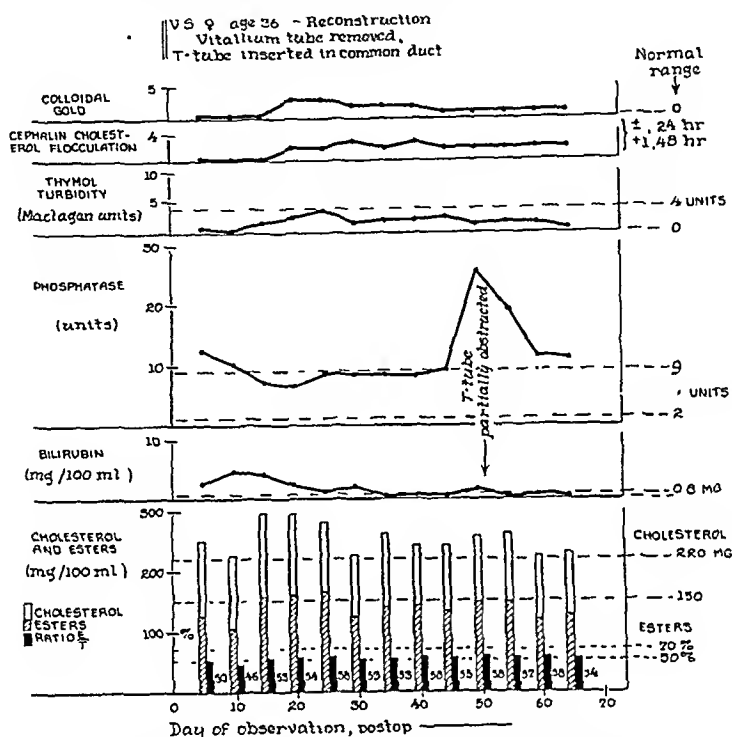


FIG. 4. Case of mild obstructive jaundice. The lesser sensitivity of the thymol turbidity test compared with that of the Hanger and colloidal gold tests actually gives it a greater specificity for the differentiation of obstructive and hepatocellular jaundice, as illustrated in this case of obstructive jaundice. The extreme sensitivity of the serum alkaline phosphatase concentration to obstruction in the biliary tract is shown by the sharp rise in its concentration when the T-tube became partially obstructed. The rise occurred with no significant change in serum bilirubin. In hepatocellular jaundice we consider the serum alkaline phosphatase level a measure of the degree of cholangiolar (Watson) jaundice present. The results of the very recent histochemical studies of Wachstein and Zak²⁶ of alkaline phosphatase in the liver in biliary obstruction support the view that the increase of serum phosphatase in liver damage is due to disturbed excretion of the enzyme.

dition of the reagent and again at eighteen hours, after allowing the specimen to stand undisturbed at room temperature. These readings were expressed as a ratio and the turbidity of the supernatant at eighteen hours recorded as a percentage of the half hour turbidity reading.* The following table gives the results in a case of hepatitis in

normal readings of the test in units and the gradual disappearance of precipitate at eighteen hours.

The complete disappearance of precipitate at eighteen hours may indicate that the serum protein fractions have finally returned to normal and that the production of normal serum protein fractions by the liver is the last function to recover completely after acute diffuse hepatic damage.

* We have called this result the "18-Hour Turbidity Ratio."

The mechanism of the thymol turbidity test has not been established. MacLagan¹⁹ studied the composition of the precipitate and found it to consist of a protein-thymol-phospholipid complex. He believes it probable that the protein is gamma globulin.

obtained a normal response in all of forty healthy young doctors and nurses and Watson and Rappaport²¹ in thirty-one presumably normal individuals.

With the simplified method for colloidal gold, MacLagan¹⁷ found no positive reactions

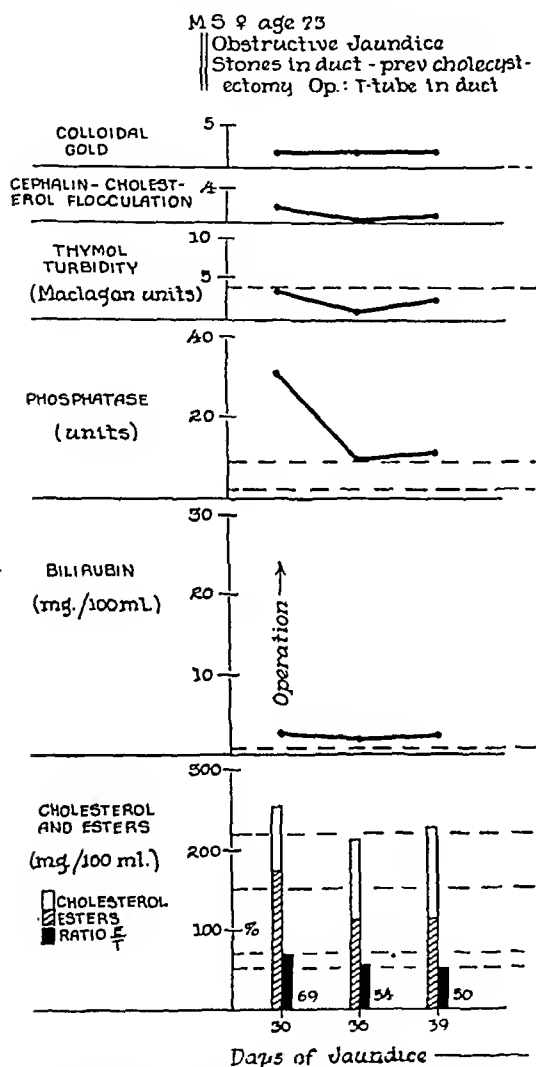


FIG. 5. Obstructive jaundice illustrating the sharp drop in serum phosphatase after bile drainage is established.

From a comparative study of the Hanger and MacLagan tests in liver disease, Watson and Rappaport²¹ concluded that the underlying mechanism of the two tests is not identical.

In normal individuals very satisfactory results have been reported for all three flocculation tests. Hanger¹¹ reported only one positive result with the cephalin cholesterol flocculation in over 900 sera. Mateer et al.¹⁸

TABLE II

Date 1946	Mg./% Serum Bilirubin	Units $\frac{1}{2}$ Hr. Thymol Turbidity	Units 18 Hr. Supernatant	Percentage of Turbidity of Supernatant—18 Hr.
5/9		3.8	1.2	32
5/13		3.4	0.9	27
5/20		2.9	0.7	24
5/27		3.0	1.2	40
6/3		2.9	1.2	40
6/10		2.6	1.5	58
6/17		2.4	2.0	83
7/27		1.8	1.4	78

with sera from normal persons and in thirty-one normal individuals Watson and Rappaport²¹ obtained readings below 4 units with the thymol turbidity test.

We considered it desirable to test the relative sensitivities of these three tests on sera from patients with gastrointestinal symptoms but with no discoverable liver disease. In seventy-six patients with functional or organic gastrointestinal disease other than liver disease, the cephalin cholesterol flocculation test was positive in seven (9.2 per cent). The colloidal gold test was positive in thirty-eight (50 per cent), in twenty of which the reading was +1. The thymol turbidity test was normal in all. Included among the seventy-six patients were fourteen cases of gallstone disease. These results suggest that the thymol turbidity test will probably have a greater specificity than the Hanger or colloidal gold test in the differential diagnosis of hepatocellular and obstructive jaundice. The data in Figures 4 and 5 indicate such a probability. These results also support the conclusion of Watson and Rappaport²¹ that the underlying mechan-

isms responsible for the flocculation reactions are not identical.

Tests Affected Primarily by Obstruction in the Biliary Passages. Many investigators have confirmed the original report of Roberts²³ of an increase in the alkaline phosphatase ac-

cnital atresia of the bile ducts to produce a rise in alkaline blood phosphatase, we have found the activity of this enzyme to be the most sensitive indicator of obstruction in the biliary passages. It is much more sensitive than changes in the serum bilirubin

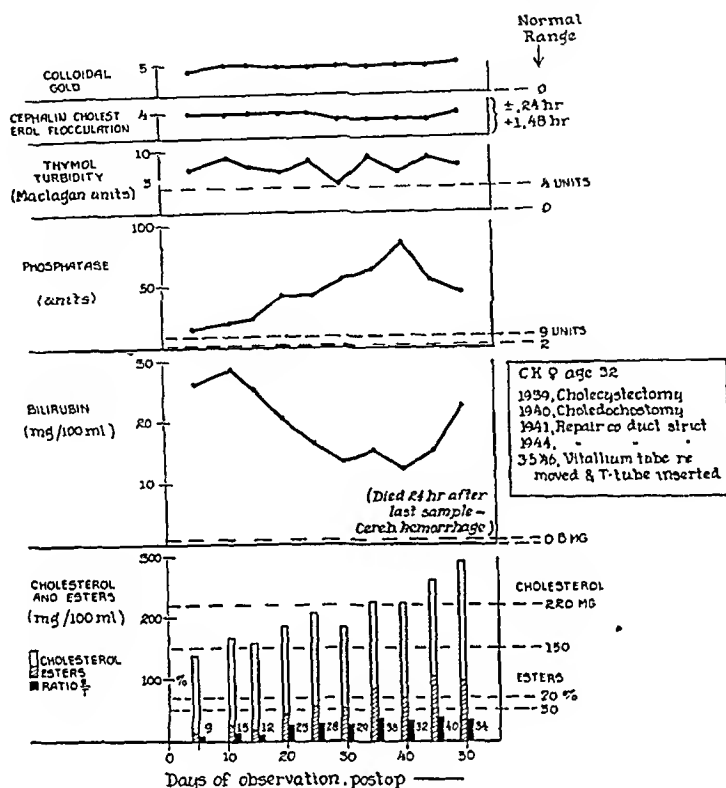


FIG. 6. Case in which multiple operations on the biliary tract had failed to cure jaundice. Exact duration of jaundice before last operation could not be determined. The results of liver function tests at this time showed that a severe degree of hepatic cell damage had developed. Such results of functional tests are a contraindication for surgery.

tivity of the blood in obstructive jaundice. The fact that relatively high readings may at times be observed in hepatocellular jaundice has created some doubt of the value of this test in icterus. Actually, when the alkaline phosphatase activity is studied serially in conjunction with the other tests suggested it helps to picture the shifting scene in the dynamic process of liver function. The effect of the variable and varying degree of canalicular obstruction (cholangiolar jaundice—Watson) that is present in practically all cases of hepatocellular jaundice will be mirrored in the changing serum phosphatase activity. Despite the failure of con-

levels. (See effect of partial T-tube obstruction, Figure 4, or result of common duct drainage on phosphatase activity and serum bilirubin levels, Figure 5.)

The increase in serum alkaline phosphatase seen in hepatic carcinoma, often in the absence of increased serum bilirubin, may be an expression of the striking sensitivity of the blood phosphatase concentration to obstruction. In such cases the growth may obstruct enough bile canaliculi to cause elevation of the phosphatase but may not involve sufficient bile channels to cause an increase in serum bilirubin. Another mechanism may be metastasis to the hilus nodes

with constriction of the common duct, sufficient to raise the pressure in the biliary tree to increase the blood phosphatase level but not the serum bilirubin level. Gutman, Olson, Gutman and Flood²⁴ have suggested that a rise in serum phosphatase in the ab-

TABLE III

TYPICAL RESULTS IN JAUNDICE WITH TESTS SUGGESTED
Obstructive Jaundice

1. Total serum cholesterol increased
2. Alkaline serum phosphatase increased considerably
3. Cholesterol ester ratio normal
4. Cephalin cholesterol flocculation normal. Not over \pm at twenty-four hours nor more than +1 at forty-eight hours
5. Colloidal gold test (Maclagan) normal
6. Thymol turbidity test less than 4 units
7. Galactose tolerance normal; urinary output below 3 Gm.

Hepatocellular Jaundice

1. Total serum cholesterol normal or only moderately increased
2. Alkaline serum phosphatase normal or increased slightly
3. Cholesterol ester ratio decreased
4. Cephalin cholesterol flocculation more than \pm at twenty-four hours, and more than +1 at forty-eight hours
5. Colloidal gold test (Maclagan) +1 to +5
6. Thymol turbidity test more than 4 units
7. Galactose tolerance—urinary output more than 3 Gm.

sence of an increase in the serum bilirubin may be dependent upon the excretion of bile in the urine and the impermeability of the human kidney to phosphatase. The limitations imposed upon the use of the serum phosphatase level as an indicator of biliary tract obstruction by certain skeletal disorders and the increased and varying phosphatase level seen in the normal growing child are discussed in the very complete report of Gutman and his associates.²⁴

In a previous study of jaundice we⁹ used the Kay-Roberts method for the determination of serum alkaline phosphatase. With that method the normal range for adults was 4 to 7 units. In hepatocellular jaundice we found that the serum alkaline phosphatase would generally remain below 15 units, while in obstructive jaundice a reading above 20 units was the usual finding. We have since changed to the Shinowara, Reinhart, Jones²⁵ technic, which gives results in

modified Bodansky units, since the pH of the buffer is higher (pH 10.7) than the Bodansky buffer (pH 9.3). By this method the normal range for adults is 2 to 9 units. With this technic we have found that our readings for hepatocellular jaundice and for obstructive jaundice to fall in ranges similar to those which we obtained with the Kay-Roberts method.

CONCLUSIONS

If satisfactory laboratory facilities are available, we believe that a minimum yet adequate liver function study may be made in jaundice with the following tests: (1) quantitative van den Bergh, (2) serum cholesterol partition, (3) serum alkaline phosphatase, and (4) thymol turbidity (electrophotometrically). *This program, in addition to including the types and number of tests considered necessary in our opening discussion of the problem, has other advantages. All of the tests are made on the same sample of blood serum, thus assuring the same environmental conditions for the collection of the materials to be tested. The problem of nursing care, as regards the collection of test materials, is simplified and errors that may occur when multiple samples must be collected can be avoided. (Table III.)

We consider the above program the minimum procedure adequate for the study of jaundice. Should the physician have only very limited laboratory facilities available, he can still follow a case of jaundice with considerable confidence by combining (1) the methylene blue test, (2) the galactose tolerance test and (3) the thymol turbidity test. For these tests, pipettes, test tubes, a Bunsen burner and a set of Kingsbury standards will supply all the laboratory equip-

*Subsequent experience with the cephalin flocculation test has shown, however, that in homologous serum jaundice a positive test may be obtained in sera giving a negative reaction with the thymol turbidity test. Because of this it would seem advisable to include the cephalin flocculation test in the routine testing of sera.

ment necessary. Table III summarizes the characteristic results obtained in the two types of jaundice with the tests suggested, omitting those used to measure the intensity of icterus.

We are convinced that a judicious selection of liver function tests will clearly and almost invariably indicate the type of jaundice present. Applied *early* in the course of jaundice and repeated at short intervals (three to four days for a period of a week, i.e., three sets of readings) the tests indicated will usually permit identification of the type of jaundice. If such studies are continued at four to seven day intervals, a much sounder prognosis is possible than that gleaned from clinical observation alone. The investigator may thus take due cognizance of the multiplicity of liver functions, the "dissociation" of the effects of liver damage upon these functions and the dynamic quality of liver function, inadequate appreciation of which has led to so much unjustified criticism of liver function tests. Attempted evaluation of an isolated liver function test in jaundice is without meaning.

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"Blast Hypertension"

*Elevated Arterial Pressures in the Victims of the Texas City Disaster**

ARTHUR RUSKIN, M.D., OWEN W. BEARD, M.D. and RANDOLPH L. SCHAFFER, M.D.

Galveston, Texas

DURING ministrations to the blast victims of the Texas City disaster we were struck by the high incidence of hypertension reaching, in extreme cases, systolic levels of 210 to 230 mm. and diastolic levels of 140 to 160 mm. Dr. E. J. Lefeber and other physicians working in the various city hospitals noted the same phenomenon. The finding of hypertension in the young, even in children, was particularly striking.

While hypertension resulting from physical or psychic trauma has been previously emphasized¹ and is usually interpreted as "neurogenic" in origin, World War II medical reports in American literature have failed to note an increased incidence of hypertension in the Armed Forces.² European observers, however, have recognized and reported this phenomenon.³ The first of such reports appeared in 1943 from the Russian front where Gelshtcin^{2a} noted the presence of hypertension (over 140/85) in 12.3 per cent of front line troops with decreasing incidence in those further removed from the battle zone. Other Russian workers also observed the marked increase of severe, often deadly, but frequently reversible forms of "neurohypertension" in young individuals under war conditions.^{3a} Later, Ehrstrom^{3b} reported what he termed psychogenic "Kriegshypertonien" ("war hypertension") from the Finnish front. He noted systolic hypertension of 150 mm. plus in 23 to 28 per cent of the front line soldiers; in more than one-half of these the diastolic pressure was also elevated. The less war-like the milieu, the lower was the incidence of

hypertensive states, the least amount occurring in civilians not engaged in war work. Finally, among members of the armored brigade in the Western Desert campaign against Rommel, a diastolic "battle" pressure over 100 mm. was noted in 26.9 per cent and a systolic pressure of over 160 mm. in 38 per cent of the British soldiers studied. Of thirty-three diastolic hypertensive patients, twenty-eight reverted to normal pressures when re-examined two months later.^{3c}

Many decades ago, Pavlov experimentally produced transient "neurogenic" hypertension by stimulating the sciatic nerve of a dog.^{3a} Recently, prolonged and nearly continuous stimulation of the renal nerves of dogs by means of the sinusoidal current has been shown to produce more lasting hypertension.^{4a} A closer reproduction of the Texas City blast hypertension is the successful maintenance of prolonged hypertension in the rat by repeated and nearly continuous air blasting.^{4b}

OBSERVATIONS IN THE TEXAS CITY DISASTER

The docked ship *Grandcamp*, loaded with ammonium nitrate, exploded at 9:12 A.M., April 16, 1947. The nearby Monsanto Chemical plants, including the Styrene building, were next blasted apart at 9:15 A.M. It has been estimated that the force of the explosions approached that of the Bikini atom bomb. It is indeed remarkable that many people near the ship and the plants survived at all. Of 408 victims treated at the John Sealy Hospital on the day of the explosion, we studied 180 who had good

* From the Departments of Medicine and Pediatrics, University of Texas Medical School and the Heart Station of John Sealy Hospital, Galveston, Tex.

hospital records with frequently recorded blood pressures. These were bed patients suffering from contusions, lacerations, ruptured ear drums, simple and compound fractures and, in some instances, cerebral and visceral injuries. In many cases, but

TABLE I
AGE INCIDENCE OF THE 180 TEXAS CITY BLAST PATIENTS

Age	1-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	Un- known	Total
No.	2	20	47	57	20	16	8	4	6	180

not in all, the same nurse, doctor or medical student took most of the readings. We performed cold pressor tests on fifty-four of the still-hospitalized patients ten to thirteen days after the blasts. There were 148 men (thirty-two negro) and thirty-two women (four negro). The age incidence is shown in Table I; the majority were young men twenty to forty years of age. Past and family histories of hypertension and its complications, which are still being carefully gathered from the patients, their families and company records, were positive in less than 20 per cent of the total group. This was confirmed by the absence of even grade I retinal arteriosclerosis or electrocardiographic signs of left ventricular strain in the great majority of patients examined.

RESULTS

Table II classifies the highest levels of systolic and diastolic blood pressure reached in each of the 180 explosion victims at any time of their hospital stay. It will be noted that systolic pressures of 150 mm. and over were attained in 90 of the 180 patients. More noteworthy is the fact that diastolic hypertensive levels of 95 mm. and over occurred in 103, or more than one-half the patients; not infrequently (in 30 of the 103) without concomitant systolic hypertension. In only thirty-five were the diastolic pressures consistently below 86 mm.

For comparison we studied the records of one hundred consecutive patients, not blast victims, hospitalized on the surgical services in the two to three months preced-

ing the disaster. It was a rather surprising fact that 34 per cent showed diastolic blood pressures of 95 mm. and over at one time or another. (Table III.) Although this percentage of hypertension was much

TABLE II
SYSTOLIC AND DIASTOLIC MAXIMA OF 180
VICTIMS OF THE TEXAS CITY EXPLOSIONS

	Systolic Pressure 150 mm. or More	Systolic Pressure 149 mm. or Less	Total
Diastolic pressure 95 mm. or more	73	30	103
Diastolic pressure 86-94 mm.	12	30	42
Diastolic pressure 85 mm. or less	5	30	35
Total	90	90	180

TABLE III
SYSTOLIC AND DIASTOLIC MAXIMA OF ONE-HUNDRED
PATIENTS HOSPITALIZED ON THE SURGICAL SERVICES IN 1947

	Systolic Pressure 150 mm. or More	Systolic Pressure 149 mm. or Less	Total
Diastolic pressure 95 mm. or more	21	13	34
Diastolic pressure 86-94 mm.	2	48	50
Diastolic pressure 85 mm. or less	2	48	50
Total	25	75	100

TABLE IV
COLD PRESSOR TESTS IN FIFTY-FOUR HOSPITALIZED PATIENTS
TEN TO THIRTEEN DAYS AFTER THE DISASTER

Postexplosion Diastolic Maxima	Positive (diastolic pressure, rise 17 mm. or more)	Border- line (di- astolic pressure rise 14-16 mm.)	Negative (diastolic pressure rise 13 mm. or less)	Total
95 mm. or more	26	7	3	36
86-94 mm.	8	0	3	11
85 mm. or less	5	1	1	7
Total	39	8	7	54

below that of our blast patients (57 per cent), this may indicate that hypertensive agents, such as psychic and operative trauma, may operate in the general surgical group of patients.

In some blast victims, elevated blood

in origin. Some blast victims likewise showed transient postoperative hypertension in previous hospital admissions.

The great majority of the blast victims, however, first presented hypertensive levels two to twenty-eight, generally seven to

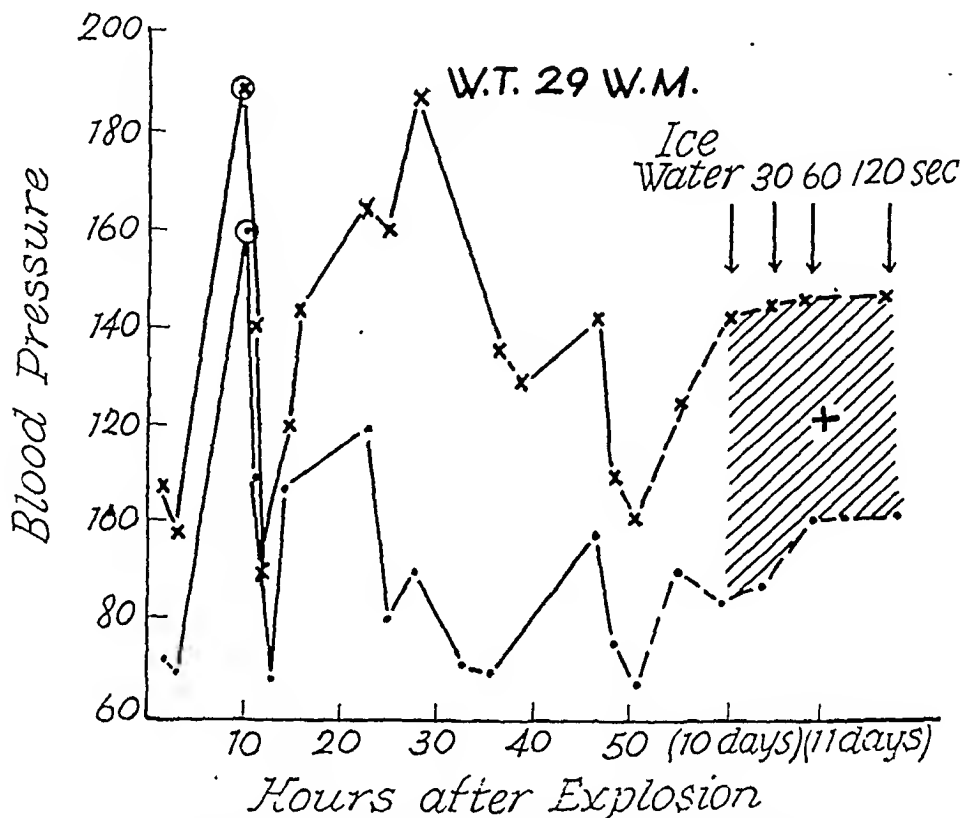


FIG. 1. W. T., twenty-nine, a white male, whose family and past histories were negative for hypertensive and allied states, was knocked down, without unconsciousness, on the ground floor of the Monsanto Office Building at the time it exploded and suffered multiple generalized lacerations with severance of the left ulnar nerve. He was given 32 mg. morphine and 1,000 cc. plasma and 1,000 cc. blood. Diastolic, 160 mm. ten hours after the blast; smaller rises occurred in the next few days. Eleven days later, blood pressure was 142/82, rising to 146/100 following immersion of forearm in ice water; the cold pressor test was positive.

pressures were found as early as one hour after the explosions; in others, they occurred postoperatively. This was so striking in isolated instances that we have made a preliminary study of fifty consecutive patients, not known hypertensives, operated upon on the surgical services in the same month as the blast victims. We found fourteen (28 per cent) showing temporary diastolic pressure rises to 95 mm. and over (as high as 120 mm.) and four others reaching 86 to 94 mm. Several showed high preoperative readings, possibly emotional

eight, hours after the explosions. (Figs. 1, 2 and 3.) In not a few patients admitted in various degrees of shock, the blood pressure rose, often to markedly supernormal levels, before returning to normal. In these patients, neither the administration of anti-shock drugs, nor of plasma, blood or other intravenous fluids (amounting often to 2 L. within several hours) appeared to influence the blood pressure curves. Following their use, the blood pressure varied too much to ascribe the hypertension to them. The length of the hypertensive state was very

variable in different individuals. The great majority presented several peaks of elevated arterial tension. They also showed generally normal blood pressures ten to fourteen days after the blasts although their cold pressor tests were usually positive

of them suffered from relatively minor injuries.

Figure 4 shows the detailed maximal blood pressure responses of the entire group. At the top of the skew curves we find systolic blood pressure levels as high as

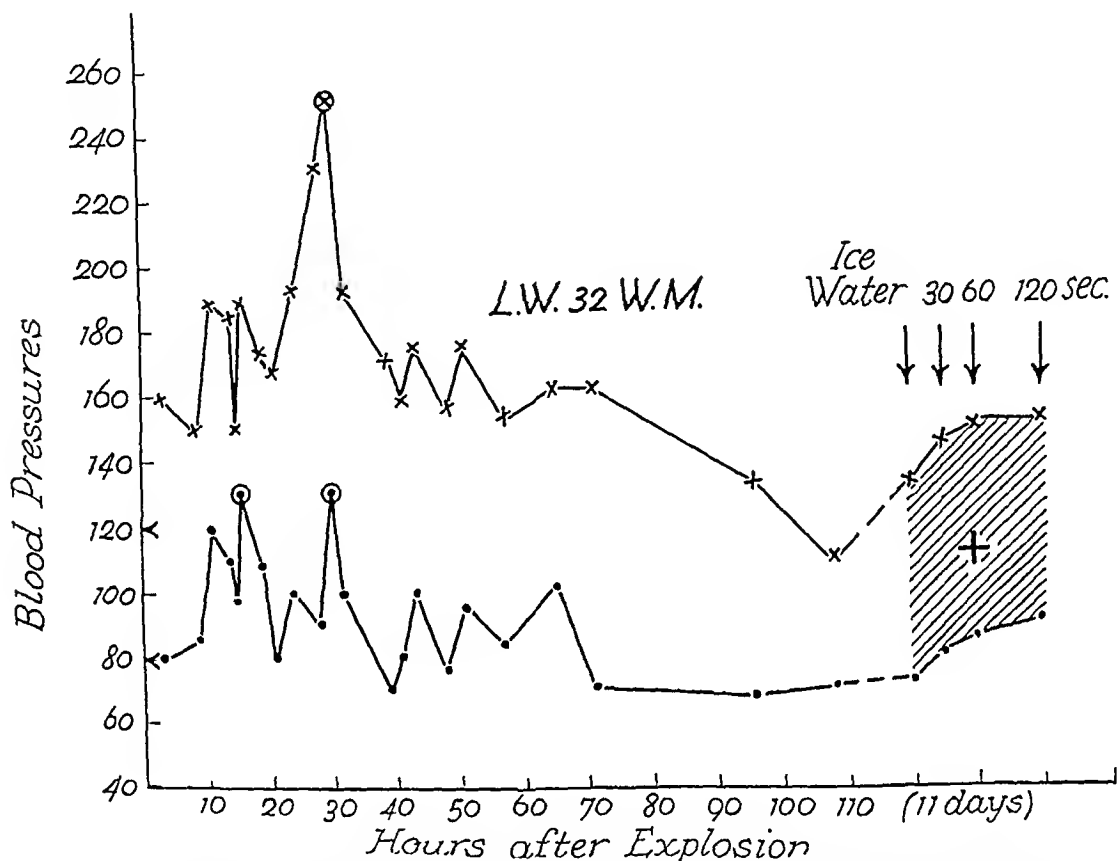


FIG. 2. L. W., thirty-two, white male, whose family and past histories were negative for hypertensive and allied states, was blown down, without unconsciousness, outside a warehouse 75 yards from the exploding ship. He sustained fractures of the left femur and right sixth and seventh ribs, with numerous lacerations. He was given 33 mg. morphine and 500 cc. plasma, 1,000 cc. 5 per cent glucose in saline during the first twenty-four hours. Systolic maximum pressure was 250 mm., diastolic 130 mm., thirty hours after the blast; smaller rises occurred before and after this time. Paroxysmal A-V nodal tachycardia was present five days after the explosions. The cold pressor test was positive (100/74, rising to 145/92) eleven days after the blast.

(Table iv) and minor diastolic elevations (around 90 mm.) were frequent at that time.

Whereas negroes presented diastolic reactions of 95 mm. plus in twenty-five of thirty-six cases, the corresponding figures for whites were 78 of 154 cases. This is of interest in connection with the well known high incidence of essential hypertension in the negro population. Women presented diastolic pressure readings of 95 mm. and over in fifteen of thirty-two patients; most

235 mm. and diastolic levels as high as 160 mm. Hg. Those patients showing the highest elevation of blood pressure did not have an appreciably greater incidence of positive past and family histories of hypertensive states than that of the total group. At the bottom of the skew curves, among the systolic levels of 110 to 130 and diastolic maxima of only 70 to 90 mm., are found many of those patients who succumbed to their injuries. Thus, three of twelve patients

with maximal diastolic values of 70 to 79 mm. died in shock despite huge quantities of intravenous fluids. If cases of severe fatal shock were subtracted from the total, the percentage of hypertensive states would be greater. Other subjects were false hypo-

reactors in that their hypertensive phase may have been missed through infrequent blood pressure recordings.

From Table iv it is seen that we obtained positive cold pressor tests in thirty-nine of fifty-four patients until two weeks after the

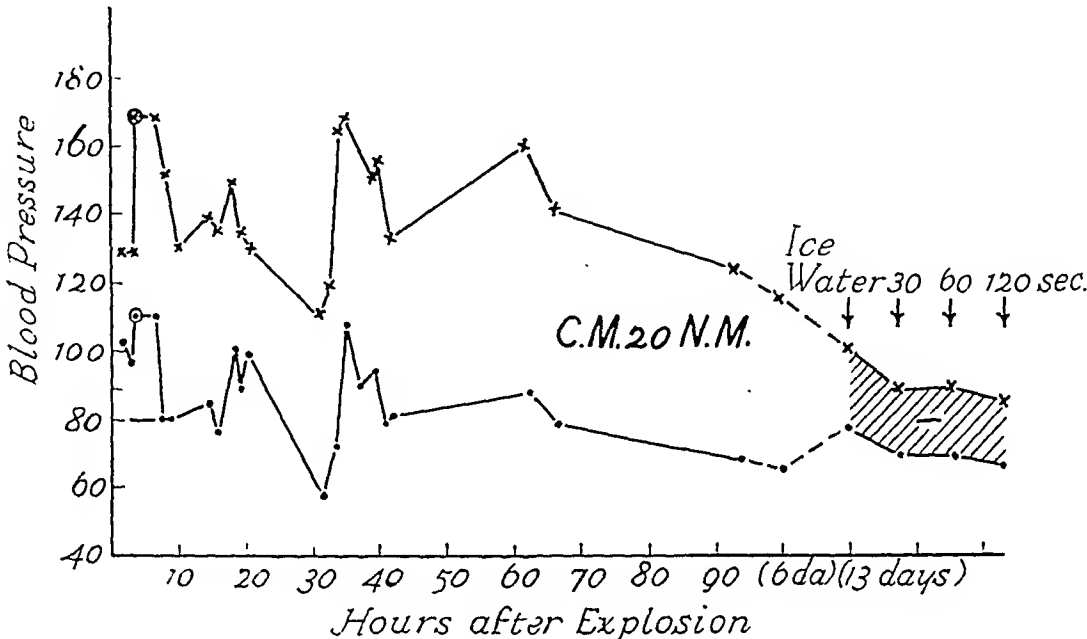


FIG. 3. C. M., twenty, negro male, whose family and past histories were negative for hypertension, had had low blood pressure according to company records. He was knocked unconscious for one-half hour as he was sitting 50 yards from exploding ship. He sustained compound comminuted fracture of the left femur, avulsion fracture of right ulnar styloid, multiple lacerations of arms and cerebral concussion (?). He received small amounts of morphine and fluids. The systolic maximum pressure was 172, diastolic 110, four hours after the blast; smaller rises occurred in the next few days. The cold pressor test was negative (100/75, falling to 85/65) thirteen days after the blast.

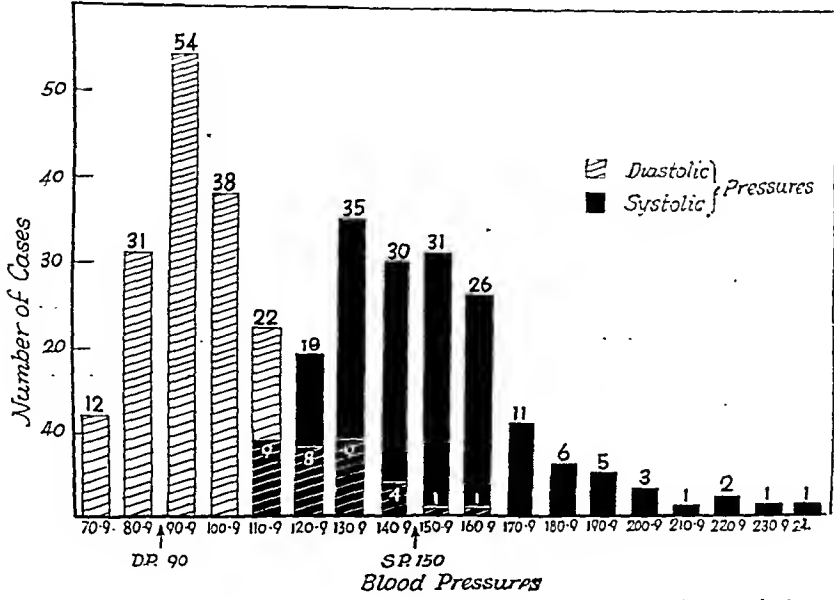


FIG. 4. Systolic and diastolic maxima of 180 victims of the Texas City explosions.

explosions. This is all the more significant since in the same fifty-four patients, thirty-six, or practically the same number, presented diastolic reactions of 95 mm. plus soon after the explosions. Likewise, while in seven patients the cold pressor tests were

emphasize, among other things, that the cold pressor responses do not mirror the height of the blood pressure obtained under other circumstances and that they may be negative with a positive family history and vice versa.

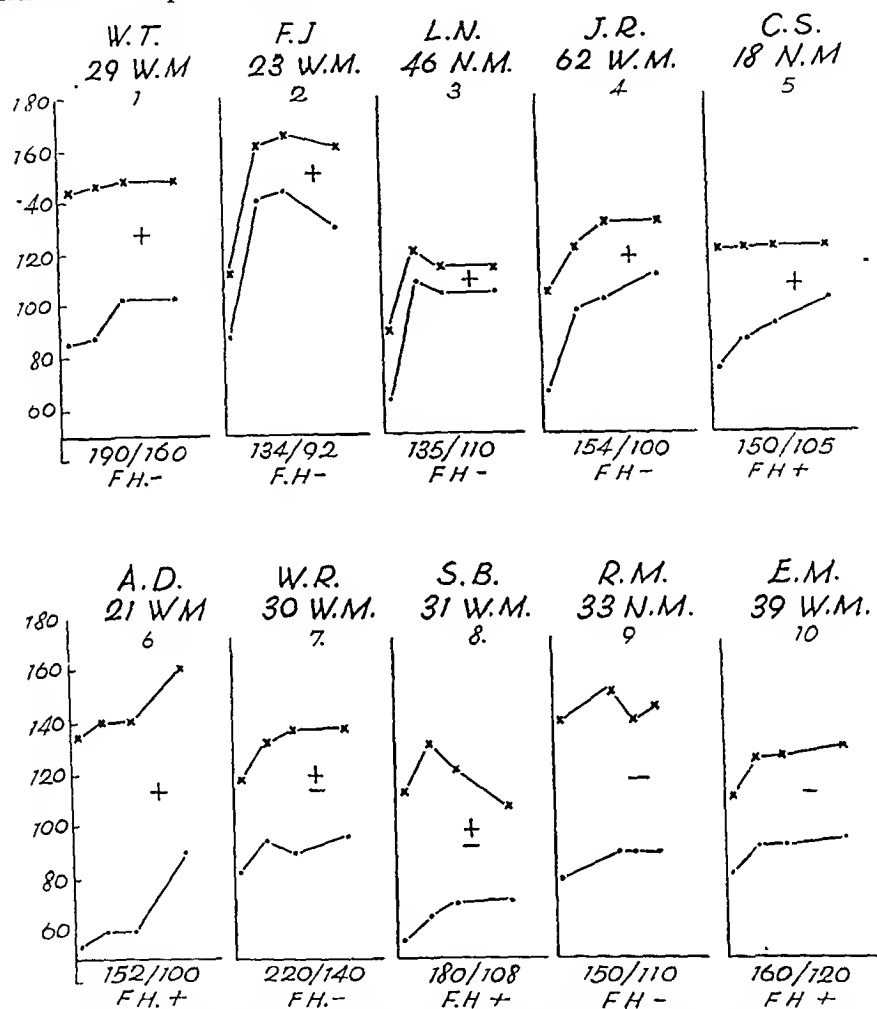


FIG. 5. Cold pressor responses of ten representative cases: six hyper-reactors, four with negative, two with positive, family histories (cases 1 to 6); two borderline reactors, one with negative, one with positive family histories (Cases 7 and 8); two hyporeactors, one with negative, one with positive family history of hypertension.

negative there were also seven patients that showed no diastolic hypertensive trend. However, as shown in Table IV, there was no parallelism between the hyper-reaction to ice water and the presumed hyper-reaction to the blast injuries. Thus, negative cold pressor tests were obtained in some patients showing high postexplosion diastolic pressures and vice versa.

Some examples of the actual cold pressor responses are shown in Figure 5. They

COMMENTS

Ehrstrom^{3b} found a systolic hypertension of 150 mm. plus in 28 per cent of the Finnish soldiers hospitalized for various reasons and brought directly from the front battle lines. Our figure of 50 per cent (Table II) is higher, probably as a result of the relatively greater effects of the blasts on our patients. For the same reason our hypertensive incidence is higher than that which Gelshtein^{3a} gives

for the Russian front line troops. At first we attempted to correlate the hypertensive reactions with the crudely classified degrees of physical injury that our patients suffered. We failed to do so. All we can say is that at the State Psychiatric Hospital, where some minor casualties were seen and quickly dismissed, diastolic hypertension of 95 mm. plus (100 mm.) was noted in only one of twelve thoroughly documented, and of thirty-six total cases. It was also our impression that patients, many of them women, slightly injured in their homes and far removed from the blast area helped to swell the hyporeactor group. On the other hand, many patients with simple contusions and lacerations were among those with the most marked systolic and diastolic elevations.

Neuropsychiatric Factors. Intracranial injuries, which if one can judge from the great frequency of draining ears⁵ and confused states, were probably more prevalent than the absence of focal neurologic signs or x-ray evidences of skull fractures would indicate, must be considered in the etiology of the postexplosion hypertensive state in our patients. While traumatic cortical lesions, subarachnoid and intraventricular hemorrhage and other intracranial conditions have been blamed for "neurogenic" hypertension,^{1a} their existence in our patients is problematic except in a few seriously injured patients, several of whom died without any hypertensive phase at all.

"Neurogenic" hypertension resulting from pain (as in one of our patients with a severe burn showing fairly continuous distress and hypertension) or great fear or anxiety, is rendered less likely by the remarkable stoicism of the victims in the first few days following the disaster and the routine use of morphine and paraldehyde. Unrelieved anoxia, asphyxia (as from respiratory obstruction) or marked restlessness were not present in more than a few of our patients. That "neurogenic" hypertension can occur even in uninjured front line soldiers,³ as well as in students before examinations,^{3b} cannot be denied. Can it reach the levels that were shown in a few

of our patients? Fishberg⁶ quotes Otto Mueller's case of "psychogenic" hypertension of 280 mm. systolic, followed after successful settlement of the mental conflict by years of normal blood pressure.

Renal Factors. Involvement of the kidneys apparently played a minor rôle in our patients. One patient in the series with renal trauma and hematuria did present a hypertensive phase. Hypertension in traumatized kidneys is not frequent, however.^{7a} It is conceivable, on the other hand, that those patients who passed through a shock phase had developed, as a result of decreased renal pulse pressure, various circulating vasoconstrictor substances.^{7b,c} How are they, as other hormonal substances suggested below, to explain the continuous and rapid fluctuations of blood pressure from hypertensive to normal or hypotensive levels seen in many of our patients? Patients with prolonged shock were very infrequent in number and they usually died without any hypertensive phase at all. Patients demonstrating anuria, oliguria, hemoconcentration or urinary abnormalities were likewise rare. Only one patient, presenting terminal slight hypertension (146/100), died in uremia, presumably the result of "crush injury" of the pelvis; this was the only patient who showed azotemia of any degree. No other cases of ischemic muscle necrosis with renal insufficiency and hypertension^{7d} developed in our series. However, "psychogenic vasoconstriction of the kidney," not excluding emotional hyperadrenalemia as a cause and resulting in a fall in the renal blood flow of as much as 40 per cent,^{7e} could easily give rise to vasoconstrictor substances originating in the temporarily ischemic kidneys.

Adrenal Factors. The rôle of the adrenal glands must always be considered in traumatic cases. Epinephrine secretion, accompanied by a rise in blood pressure and heart rate, staring pupils, pallor, etc., was considered the main factor in the "alarm reaction" by Cannon^{8a} and in "battle" hypertension of the British troops in Africa

by Graham.^{3c} Transient hyperadrenalemia could easily play a part in the general sympathetic overactivity in our patients but would account mainly for elevation of systolic pressures.

Arteriolar vasoconstriction, from whatever cause, certainly exceeded increased cardiac output among the compensatory phenomena inasmuch as diastolic hypertension occurred more commonly than, and often independent of, systolic hypertension. In general, marked compensatory hypertension was prognostic of survival and failure of vasoconstriction, as evidenced by constant low diastolic pressures, frequently led to death in our shocked patients. The finding of hypotension, normotension and hypertension in all degrees and proportions in many patients who presented the clinical picture of traumatic shock corroborates the experimental and clinical evidence pointing to lack of consistent hypotension in surgical shock except in its terminal or irreversible phases.⁹ As clinical shock was present in only a portion of the series, it cannot of itself be held accountable for the more generally prevalent hypertensive states.

Selye^{8b} has recently proposed that in the "resistance phase" of the "adaptation syndrome" to "noxious stimuli," the rise in blood pressure, sometimes to hypernormal levels, results from adrenal cortical oversecretion in animals. Such a theory, if true, would explain the finding of hypertension following shock in some of our patients. Hypervolemia and hypertension have been demonstrated in human subjects following the use of desoxycorticosterone.^{8c} There is no direct proof at present that such a compensatory phenomenon occurs in human subjects following traumatic shock.

Significance of Cold Pressure Tests. The results of the cold pressor tests, even if markedly positive, speak neither for familial predisposition nor for the neurogenic or hormonal mechanism of hypertension in our subjects. Cold, being considered a "noxious stimulus," stimulates not only the sympathetic nervous system but also the adrenal glands and, presumably through

producing renal ischemia, can evoke vasoconstrictor substances from the kidney as well. The highest percentage of hyper-reactors in the general population is placed at 18 per cent by Hines^{10a} and 56.7 per cent (at sixty to sixty-nine years of age) by Russek and Zohman.^{10b} These figures are greatly exceeded by those of our patients. Will our patients hyper-react as much in the future? Russek^{10b} and Todd^{10c} among others have disproven the idea that a positive cold pressor test indicates either a positive family history or future hypertension. Why may it not mean, as in our patients, vascular over-reaction to cold as to other noxae through the medium of a temporarily hypersensitive sympathetic nervous system and, perhaps, transiently formed hormonal vasoconstrictors?

Whether the hypertensive states shown by the blast victims represent actual or latent essential hypertension cannot be affirmed or denied on the basis of our data. Future studies of our group, as well as the groups of soldiers studied abroad, are badly needed. Master,^{11a} in re-examining a group of sixty navy personnel who had shown a single reading of 140-156/77-90 from one to seven years previously, found hypertension in 74 per cent, with diastolic pressures over 100 mm. in 25 per cent. Garai^{11b} found positive cold pressor tests in twelve of fifteen shipwrecked seamen several months to one to two years after their ships had been sunk by torpedoes or mines. Controls showed positive cold pressor tests in less than one-half the patients. In our experience, as in Garai's, cold hyper-reactors are particularly common among psychoneurotic individuals.

SUMMARY

Careful observations show definite although not prolonged diastolic hypertension in the majority of the victims of the Texas City disaster. We intend to follow-up our patients and report on them in the future.

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Coexisting Auricular Fibrillation and Complete Heart Block

EDGAR A. HAUNZ, M.D.* and HARRY L. SMITH, M.D.†

Rochester, Minnesota

A FEW isolated reports of patients with conditions of auricular fibrillation coexisting with complete heart block have appeared in the literature, but so far as we know, no attempt has been made to analyze a group of such cases in search of clinical or pathologic features which they may share in common. Our curiosity was aroused particularly in finding that this combination is not especially rare.

During 1943 to 1945, inclusive, a total of ten patients at the Mayo Clinic were found to have definite electrocardiographic findings of concomitant auricular fibrillation and complete auriculoventricular dissociation. In reviewing the electrocardiographic files two instances of coexisting auricular flutter and complete heart block were also encountered but are not included in this analysis.

The concurrence of these two cardiac irregularities is disclosed electrocardiographically by the following criteria: (1) a *regular*, slow ventricular rate (usually less than 65 beats per minute); (2) absent P waves and (3) the presence of "fibrillary waves." Conversely, if complete heart block is not present with auricular fibrillation the ventricles will exhibit irregularity in rhythm; namely, the R-R intervals will not be equidistant, and the rate tends to be more rapid.

Ashman and Hull have stated that the complete heart block in this combination "is usually functional rather than due to any organic lesion." It may, of course, be purely

a digitalis effect in some cases, as will be shown presently, but it is very doubtful that any of our cases were on a so-called functional basis because in every instance there was apparent severe myocardial damage incident to either arteriosclerosis, rheumatic endocarditis or hypertension.

Because of the rarity of auricular fibrillation in children the combination of auricular fibrillation and complete heart block probably occurs exclusively in adults. So far as we know, no cases of this combination in children have been reported.

ANALYSIS OF CASES

Of the ten patients studied seven were men. The youngest patient was a man of forty-three years; the oldest who was seventy-eight years, also was a man. The average age was sixty-two years. All patients had roentgenographic evidence of marked cardiac enlargement, and similarly all had diagnoses of serious cardiac or cardiovascular disease as follows: rheumatic heart disease, four cases; hypertensive and coronary heart disease, six cases. Severe arteriosclerosis was noted in two cases. Of the hypertensive group two gave a past history of cerebrovascular accident. Seven patients either had a past history of congestive failure or were decompensated when seen at the clinic. Varying degrees of dyspnea had been experienced in all cases but one.

In three cases the complete auriculoventricular dissociation was undoubtedly due

* Fellow in Medicine, Mayo Foundation.

† Division of Medicine, Mayo Clinic.

to a digitalis effect, which does not in itself imply digitalis intoxication.

To date there have been two deaths. One death occurred following a transurethral resection, from causes unrelated to the heart. The other patient died elsewhere about seven months after dismissal from the clinic and a necropsy was not performed. The cardiac findings at necropsy in the first of these two cases (Case VIII) were as follows: (1) patent foramen ovale (4.0 by 3.0 cm.) with hypertrophy of the right auricle, grade 2 (on the basis of 1 to 4 in which 1 represents the mildest and 4 the most severe condition); pulmonary arteriosclerosis, grade 1, and dilatation; (2) healed rheumatic mitral and aortic endocarditis with calcification; (3) hypertrophy of the heart; weight 520 Gm. (normal 225 Gm.) with focal fibrosis (healed infarcts); ancient rheumatic myocarditis; (4) coronary sclerosis, grade 2

CASE REPORTS

CASE I. The patient, a man aged forty-five years, gave a history of recurrent attacks of swelling of joints since the age of sixteen years. The last attack had occurred four weeks before an electrocardiogram was taken. There had never been any dyspnea or definite evidences of congestive failure. Blood pressure on admission was 135 mm. of mercury systolic and 85 diastolic. A roentgenogram of the thorax revealed cardiac enlargement with deformity of the cardiac contour. The pulmonary fields were clear. The patient had never received digitalis. The clinical diagnosis was recurrent rheumatic fever with rheumatic heart disease (compensated).

CASE II. The patient, a man aged sixty years, gave a history of anginal pains (exertional) over the past four years. There had been a recent cerebrovascular accident followed by headaches and residua of aphasia and defect of memory. There had been some dyspnea but no actual episodes of congestive failure. Blood pressure on admission was 200 mm. of mercury systolic and 100 diastolic. A roentgenogram of

the thorax showed cardiac enlargement but pulmonary fields were clear. The patient was never given digitalis. The clinical diagnosis included coronary and hypertensive heart disease, with angina pectoris, recent cerebrovascular accident and adenomatous goiter without hyperthyroidism.

CASE III. The patient, a man aged forty-three years, gave a history of edema over the past three months, the cause of which was unknown. There had been varying degrees of dyspnea but no pain. No episodes of congestive failure had occurred. Blood pressure on admission was 115 mm. of mercury systolic and 70 diastolic. A roentgenogram of the thorax was negative except for marked cardiac enlargement. The patient had received digitalis for an indefinite period just prior to admission. The clinical diagnosis was possible interauricular septal defect, mitral stenosis (?), and paralysis of left vocal cord (possibly due to pressure from left auricle).

CASE IV. The patient, a woman aged fifty-five years, gave a history of attacks of pain in the right upper quadrant of the abdomen extending to the right shoulder, accompanied by vomiting, fever and headache. She had averaged three such attacks yearly for several years. A non-functioning gallbladder with stones was seen on roentgenographic examination. She had a history of rheumatic fever and seven weeks prior to admission to the clinic she had had a stroke with right hemiplegia from which she had apparently completely recovered. For nine months prior to admission she had complained of nocturnal dyspnea. Signs of congestive failure were in evidence on admission. Blood pressure on admission was 190 mm. of mercury systolic and 90 diastolic. A roentgenogram of the thorax revealed marked cardiac enlargement but pulmonary fields were clear. The patient had taken three capsules of digitalis daily for three months and recently noted some diarrhea and blurring of vision, which raised the suspicion that overdigitalization was the cause of the complete heart block that was present in the first electrocardiographic tracing. This suspicion was strengthened by the fact that bigeminal pulse and premature ventricular contractions were noted on a second tracing taken four hours

after the first. The heart block was absent in a third tracing taken six days later. The clinical diagnosis included hypertensive and coronary heart disease with decompensation and chronic cholecystitis with cholelithiasis.

CASE V. The patient, a man aged sixty-four years, gave a history of questionable mild cerebrovascular accident in July, 1945, with no residua. He was admitted to the clinic on October 2, 1945, complaining of mild exertional dyspnea, but no nocturnal dyspnea. There had been a previous episode of pain in the left anterior portion of the thorax, extending to the left shoulder and arm. There were no definite features of angina pectoris. No previous history of congestive failure could be obtained and there was no evidence of it on admission. Blood pressure on admission was 180 mm. of mercury systolic and 80 diastolic. A roentgenogram of the thorax at the time was entirely negative. This was of interest because a roentgenogram taken at the clinic in 1940 had disclosed a prominent left ventricle. The patient had never received digitalis. The clinical diagnosis was chronic rheumatic aortic and mitral endocarditis with aortic insufficiency.

CASE VI. The patient, a man aged seventy-eight years, gave a history of progressive weakness and failing vision. He was admitted to the clinic on July 28, 1944, in a semicomatose state and presented a nursing problem. There had been an episode of congestive failure in 1942 but none since. On admission his blood pressure was 180 mm. of mercury systolic and 90 diastolic. A roentgenogram of the thorax, taken in 1942, had shown marked cardiac enlargement. The patient had taken digitalis in the past, but none recently. The clinical diagnosis was Parkinson's disease with cerebral degenerative changes and arteriosclerosis. Auricular fibrillation with complete heart block first had been noted at the clinic in November, 1934, and was still present at the time of this examination.

CASE VII. The patient, a woman aged seventy-three years, gave a history of episodes of congestive failure since 1934 with dyspnea, edema and so forth, requiring diuretic agents and digitalis. Despite cholecystectomy in 1934 she continued to have attacks of biliary colic, characterized by pain, chills, fever and inter-

mittent jaundice since that time. She was readmitted to the clinic on April 15, 1943, at which time her blood pressure was 124 mm. of mercury systolic and 80 diastolic. A roentgenogram of the thorax had not been taken since 1940 at which time there was marked cardiac enlargement with considerable deformity of the cardiac contour. It is of interest that auricular fibrillation with complete heart block was present in three electrocardiographic tracings taken between April 15, 1943, and April 10, 1944, but that a fourth tracing taken on June 12, 1944, showed that the complete heart block had disappeared. Although she had received digitalis quite regularly since 1934 it cannot be stated with certainty that the drug induced heart block, since typical symptoms of digitalis effect were not in evidence. When the most recent electrocardiogram was taken on September 17, 1945, the heart block was still absent. This strengthens the suspicion that the heart block was a digitalis effect. The clinical diagnosis included chronic rheumatic endocarditis with mitral stenosis and insufficiency and probable common duct stone.

CASE VIII. The patient, a man aged seventy years, gave a history of edema, grade two of ankles with exertional dyspnea and occasional nocturnal dyspnea of several weeks' duration. He had had episodes of congestive failure five years and one year before admission to the clinic. He was admitted to the clinic on May 29, 1945. His condition was easily controlled by administration of digitalis since he had previously been on a maintenance dose of $1\frac{1}{2}$ gr. (0.1 Gm.) daily for five days each week. On May 30, 1945, a transurethral resection was performed for prostatic hypertrophy with obstructive symptoms. This was done with full realization of increased risk of operation. The danger consequent on the degree of urinary obstruction outweighed the cardiac risk, although a roentgenogram of the thorax showed cardiac enlargement with vascular engorgement. The patient died postoperatively from causes unrelated to the heart. The findings at necropsy have been reported earlier in this paper. The clinical diagnosis was arteriosclerotic heart disease with myocardial degeneration and benign prostatic hypertrophy.

CASE IX. The patient, a man aged sixty-five years, gave a history of edema of the ankles, orthopnea, nocturnal dyspnea and sensations of pressure in the thorax, all intermittent, over the two years prior to admission. He had had a probable coronary occlusion in May, 1941, but

CASE X. The patient, a woman aged sixty-six years, gave a history of exertional and nocturnal dyspnea, palpitation and attacks of substernal pain relieved by rest over the past two to three years. For some time she had had vomiting at bedtime and before breakfast, to-

Fig. 1 2-9-43 (10 AM)

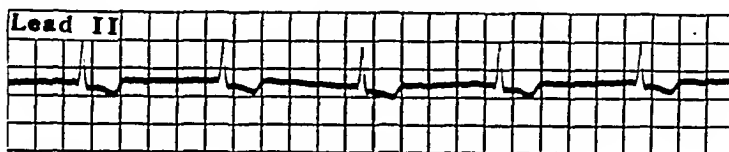


Fig. 2 2-9-43 (2 PM)

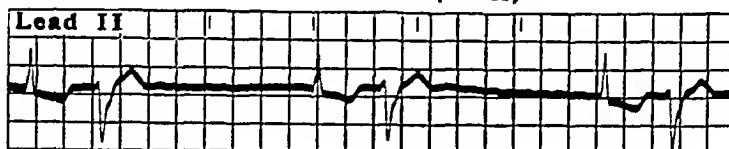
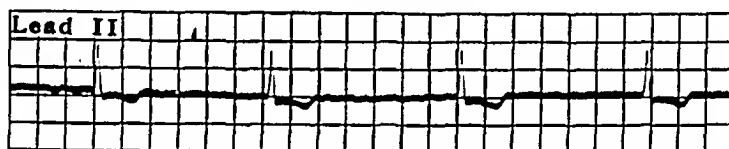


Fig. 3 2-15-43



FIGS. 1, 2 and 3. Only lead II is shown of three serial tracings taken in case IV. Figure 1 represents clearly defined auricular fibrillation and complete heart block. In Figure 2, taken four hours later, note that premature ventricular contractions (bigeminal pulse) are superimposed. Six days later (Fig. 3) all that remains is pure auricular fibrillation. The complete heart block was obviously a digitalis effect.

despite symptoms he was able to work about 50 per cent of the time. There had been several brief attacks of syncope. On admission to the clinic on May 27, 1943, he was found to have ascites, grade 2, and hepatomegaly, grade 2 (on the basis of 1 to 4). A roentgenogram of the thorax showed cardiac enlargement with fluid in the right portion of the thorax. Blood pressure was 210 mm. of mercury systolic and 100 diastolic. The patient had received digitalis intermittently in the past. He was hospitalized for thirteen days, receiving hypertonic solution of glucose, aminophylline and diuretics, but no digitalis. There was a fair therapeutic response. Digitalis was withheld because of the very slow cardiac rate of 31 in the presence of auricular fibrillation with complete heart block. The clinical diagnosis was hypertensive and coronary heart disease with congestive failure. The patient was reported dead on January 14, 1944. Necropsy was not performed.

gether with blurring of vision. These latter symptoms were obviously due to digitalis intoxication, since she had been taking 1 cat unit of digitalis daily for some time prior to admission to the clinic. There had been several episodes of congestive failure. The patient was admitted to the clinic on September 15, 1944, with obvious signs of congestive failure. Our previous electrocardiograms in this case showed that she had had auricular fibrillation without heart block in 1932 and 1935. The electrocardiogram taken on September 15, 1944, revealed auricular fibrillation with complete heart block. The heart block here was undoubtedly a digitalis effect. Roentgenographically there was marked cardiac enlargement. The patient was hospitalized on this admission and the dose of digitalis was reduced to 1 cat unit three times a week. Her symptoms improved. It is probable that the complete heart block disappeared before her dismissal, though unfortunately a second electro-

cardiogram was not taken. The clinical diagnosis in this case was arteriosclerotic and hypertensive heart disease.

COMMENT

To establish accurately the diagnosis of concomitant auricular fibrillation and com-

heart block in this series of cases have been enumerated earlier in this paper.

It has been emphasized that all ten patients had serious cardiac or cardiovascular disease. Therefore, when the heart block is not definitely due to a digitalis effect, its presence with auricular fibrillation implies

Fig. 4 4-15-43

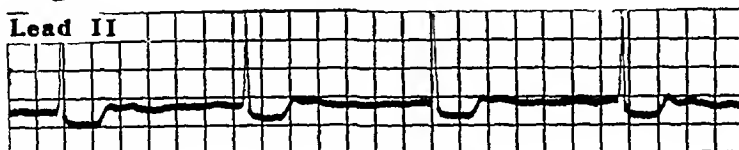


Fig. 5 3-1-44

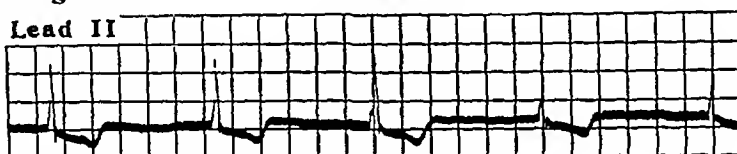


Fig. 6 6-12-44

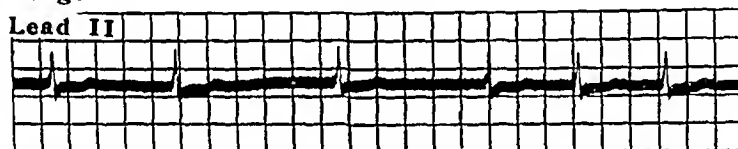
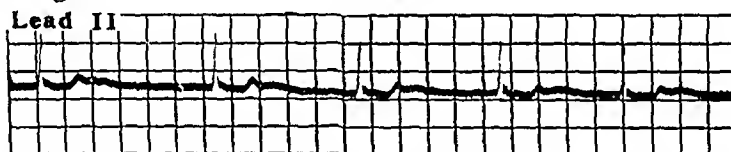


Fig. 7 9-17-45



FIGS. 4, 5, 6 and 7. Serial tracings in case VII (lead II only). The covered S-T segment in Figure 4 suggests a digitalis effect in itself. However, subsequent changes are more reliable since no coving is apparent in Figures 5, 6 and 7. In Figures 6 and 7 there is pure auricular fibrillation without heart block and this probably was stationary because the same pattern persists in the final tracing. (Fig. 7.) Tracings taken in 1934 showed only auricular fibrillation.

plete auriculoventricular dissociation one must exclude occasional cases of auricular fibrillation in which there is extreme bradycardia in the absence of complete heart block. This can be accomplished by careful measurement of the R-R intervals, which will not be uniformly equidistant in cases of pure auricular fibrillation without heart block. In other words the ventricular rate, though extremely slow, is definitely variable. The criteria used in establishing the diagnosis of auricular fibrillation with complete

serious cardiopathy and a poor prognosis. In Barnes's opinion the presence of complete heart block in the absence of auricular fibrillation carries a more favorable prognosis than a combination of the two states, even when the pathologic substrate is the same as the cause of the heart block in either case.

The value of serial electrocardiograms, taken a few days apart, is indisputable in those patients who present themselves with a history of digitalis therapy which has been

continued for some time, especially when one has not seen these patients previously. If the complete heart block in such cases is due to digitalis, subsequent tracings may show variations in pattern and if the drug is withheld the heart block should finally disappear. This point is well illustrated in Case iv. Figure 1 shows the initial tracing obtained February 9, 1943, when this fifty-five year old woman was admitted to the clinic. Auricular fibrillation and complete heart block are in evidence. In the second tracing (Fig. 2) taken four hours later, premature ventricular contractions (bigeminal pulse) are superimposed, but the heart block is still present. Finally, in a third tracing (Fig. 3) taken six days after the first, there is pure auricular fibrillation without heart block. Since the patient presented only mild symptoms of digitalis intoxication, the dissimilarity of serial electrocardiographic tracings (especially revealing the final disappearance of complete heart block) presented more tangible evidence that we were dealing with a digitalis effect. When the symptoms of digitalis intoxication are slight (as noted in this case) or absent, the presence of complete heart block in addition to auricular fibrillation does not necessarily contraindicate continuing administration of the drug, for in the presence of marked congestive failure further digitalization may be quite rational. However digitalis was withheld in the foregoing case for some time, and there was marked improvement in the patient's congestive failure in response to rest in bed, salyrgan and hypertonic solution of glucose intravenously administered.

Case vii is very similar to Case iv in that the patient presented variable electrocardiographic findings in serial tracings, except that these changes occurred over a period of nearly two years. On April 15, 1943 (Fig. 4) auricular fibrillation with complete heart block was first noted electrocardiographically (previous tracings in 1934 showed only

auricular fibrillation). This combination was still present in tracings made on March 1, 1944. (Fig. 5.) However, subsequent electrocardiographic tracings taken on June 12, 1944 (Fig. 6) and on September 17, 1945, (Fig. 7) showed a return to the original pure auricular fibrillation without heart block. In our opinion the complete heart block was a digitalis effect in this case, despite the fact that the patient apparently never had definite symptoms of digitalis intoxication.

It should be mentioned that interference dissociation may simulate complete auriculoventricular block. However, this could easily be ruled out in these cases because in the former condition the ventricular rate exceeds that of the auricles owing to a nodal or idioventricular rhythm. This rare condition is usually attributed to digitalis.³

SUMMARY

The interesting phenomenon of concurrent auricular fibrillation and complete heart block has been studied in a series of ten cases. At least two important points are to be gained from this analysis:

1. The presence of this combination, in the absence of digitalis effect, implies a serious prognosis. All ten patients had advanced cardiac or cardiovascular disease.
2. It is important both prognostically and therapeutically to distinguish between complete heart block incident to intrinsic cardiopathy and complete heart block of digitalization. In cases in which symptoms of digitalis intoxication are slight or absent the distinction can be made by observing serial electrocardiographic tracings.

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Electrocardiographic Patterns of Ventricular Aneurysm*

EMANUEL GOLDBERGER,† M.D. and SIDNEY P. SCHWARTZ, M.D.

New York, New York

IN several papers the following two electrocardiographic patterns have been described in cases of ventricular aneurysm resulting from myocardial infarction:¹⁻⁴ (1) A small r_1 associated with deep $S_{2,3}$; (2) the main ventricular deflection is downward in the three standard leads.

However, not all cases of ventricular aneurysm show these electrocardiographic patterns and these patterns may be present in the absence of an aneurysm. Furthermore the explanation for these patterns has been obscure. We recently studied all cases in which the main ventricular deflections were downward in the standard leads, using unipolar extremity leads as well as standard leads.⁵ In this paper we have studied our cases of ventricular aneurysm in the same way.

MATERIAL

A total of forty cases of myocardial infarction were selected for study. These included fifteen cases of ventricular aneurysm diagnosed clinically (by means of both fluoroscopic and x-ray studies of the heart) or at autopsy; one case of rupture of the left ventricle after infarction, confirmed by autopsy; and twenty-four cases of myocardial infarction that showed either of the above patterns, but in whom an aneurysm was absent.

METHOD

Standard leads were taken in the usual way. The unipolar extremity leads were

taken using the author's method.⁶ The author's indifferent electrode of zero potential was used for the unipolar leads.² In addition to these leads, one or more precordial leads were taken. In many of the precordial leads, the left leg was used as the indifferent electrode. In the other cases unipolar precordial leads were taken.⁶

GENERAL RESULTS

Each standard lead represents the difference between the potentials at two extremities. In spite of this fact the following relations usually exist between the standard lead and the unipolar leads that record the potentials at each of the extremities:^{7,8,9} Lead I tends to resemble the left arm lead; lead II tends to resemble the reverse of the right arm lead, and lead III tends to resemble the left leg lead.

Cases with the $r_1S_{2,3}$ Pattern. Figures 1B, C, D, E, 2 and 3C, show this pattern. Aneurysms were associated with Figures 1B, C, D and E and were absent in the other cases. When the unipolar extremity leads of these cases are studied, they show the following similar characteristics, regardless of the presence or absence of an aneurysm: (1) Infarction of the anterior wall of the left ventricle was present; (2) the left arm lead tends to show a small r wave; (3) the QRS complex of the right arm lead, which is normally downward tends to be upward, and (4) the left leg lead shows an rS pattern (a small r and a deep S wave). These characteristics can be analyzed in more detail.

* From the Medical Division, Montefiore Hospital, New York, and the Department of Medicine, Lincoln Hospital, New York.

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Left Arm Lead. When anterior infarction occurs, unipolar leads that overlie or face the epicardial surface of the infarct show a deep wide abnormal Q wave, an elevated RS-T segment and a small or absent final R wave.⁸ When anterior infarction is pres-

In the standard leads, lead I resembles the left arm lead. This produces the small r_1 .

Right Arm Lead. In Figures 1c, E and 3c the right arm lead shows a biphasic QRS complex consisting of an initial downward deflection (Q) followed by an upward de-

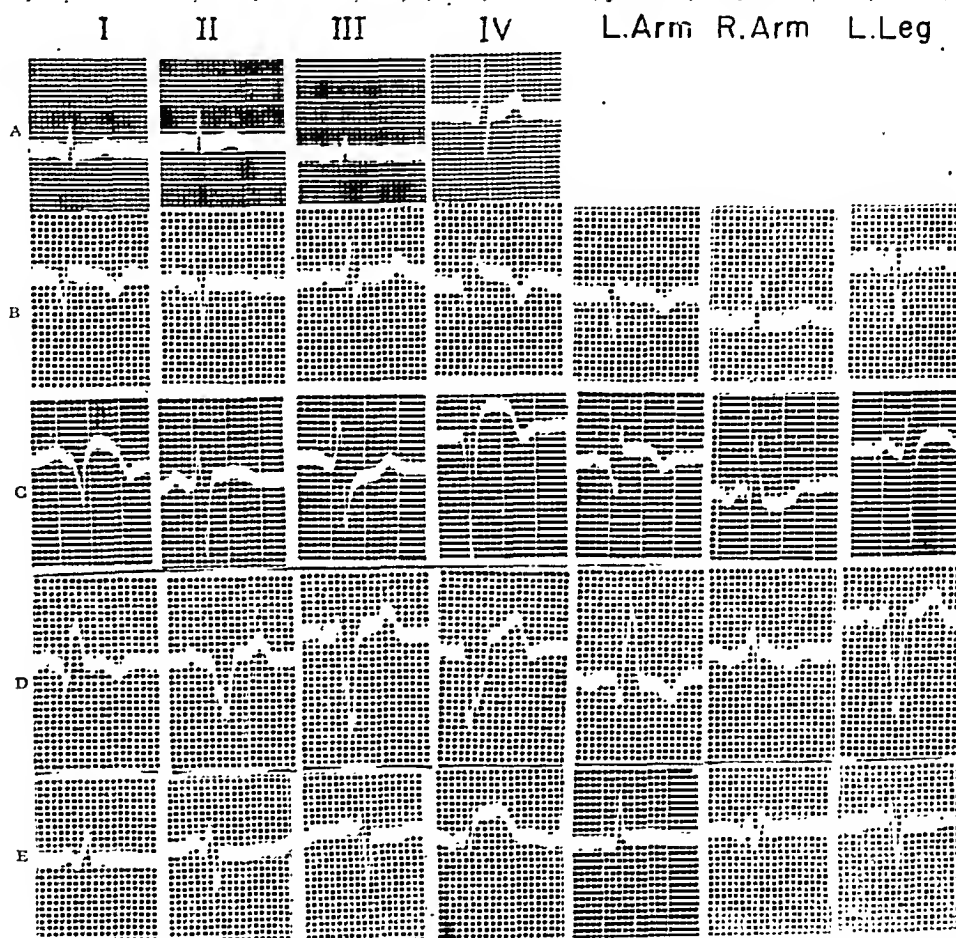


FIG. 1. Cases of ventricular aneurysm that show an $r_1S_{2,3}$ pattern. Left arm, right arm and left leg; augmented unipolar extremity leads. A, B, fifty-nine-year old man. A, taken in 1937; shortly after this he developed an anterior infarct and subsequently a ventricular aneurysm; B, taken in 1944. C, fifty-nine-year old man. D, fifty-six-year old man. E, fifty-eight-year old man. This patient died from rupture of the left ventricle. The tracing was taken the day before he died.

ent and the heart lies horizontally, this pattern is transmitted to the left arm lead.¹⁰ Figures 1B and C show this. Wilson has pointed out that the final R wave becomes tall when a unipolar lead faces the margin of the infarct. Figures 1D, E and 2 show a tall R wave in the left arm lead, in spite of the fact that the R is either absent or small in the precordial lead.

flection (R). In Figures 1B, D and 2 the right arm lead shows an initial R wave which may or may not be followed by a downward deflection.

The explanation for the QR pattern in the right arm lead is as follows: A QR pattern is normally found in one or more unipolar leads taken over the upper region of the back, or in esophageal leads above the

level of the ventricles.^{9,10} This pattern can be transmitted to the right arm when marked clockwise rotation of the heart around its long axis occurs.^{9,10} The QR pattern in the right arm lead of these cases, therefore, is not a sign of either infarction

cardial surface of the right ventricle, and shows an rS pattern, even when the heart is normal.^{9,10} In the standard leads, lead III resembles the left leg lead. This causes the deep S₃.

Figure 3 shows how the r₁S_{2,3} pattern

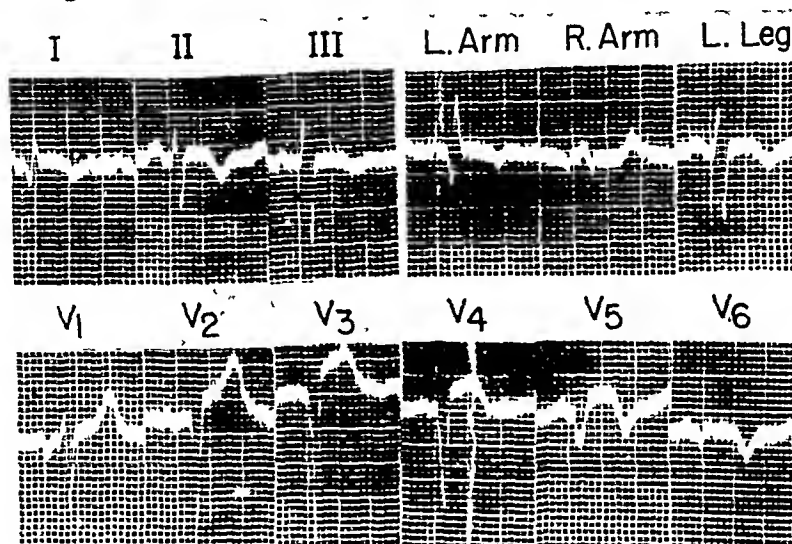


FIG. 2. Tracing that shows the r₁S_{2,3} pattern, without an aneurysm; sixty-two-year old man. V₁ to V₆ are unipolar precordial leads.

or aneurysm and merely indicates the position of the heart.

The tall initial R wave in the right arm lead is also due to the position of the heart as Figure 2 shows. Notice that in Figure 2 the right arm lead is very similar to precordial lead V₁, which is recorded from the fourth intercostal space just to the right of the sternum. The similarity between these two leads in this case can be explained by assuming that forward rotation of the heart around its transverse axis is present. When this happens, patterns found on the anterior chest wall in the region of the sternum can be transmitted to the right arm lead. Here again, this pattern is neither a sign of aneurysm nor of infarction.

In the standard leads, lead II is often the reverse of the right arm lead. It therefore shows a prominent S wave when the QRS complex of the right arm lead tends to be upward, as in the above examples.

Left Leg Lead. When the heart lies horizontally, the left leg lead faces the epi-

cardium can occur in a patient with myocardial infarction without an aneurysm. This is the tracing of a forty-three year old man who was suffering from an acute anterior infarct. Figure 3A was taken two days after the attack. Figure 3B was taken a week later. Figure 3C was taken two weeks later. The r₁, S_{2,3} pattern is present in Figures 3A and C. It had disappeared in Figure 3B. In other words, the r₁S_{2,3} pattern is a variable one and subject to change. The unipolar extremity leads show the cause of the change because in Figure 3B, in which the pattern is not present, the QRS complex of the right arm lead is downward, whereas in Figure 3C, where the r₁S_{2,3} pattern has returned, the right arm lead shows a QR pattern.

Cases in Which the Main Ventricular Deflections are Downward in the Standard Leads. Figure 4 shows such a pattern. This patient had anterior and posterior infarctions and an aneurysm of the left ventricle. Figures 1B and C, which show the

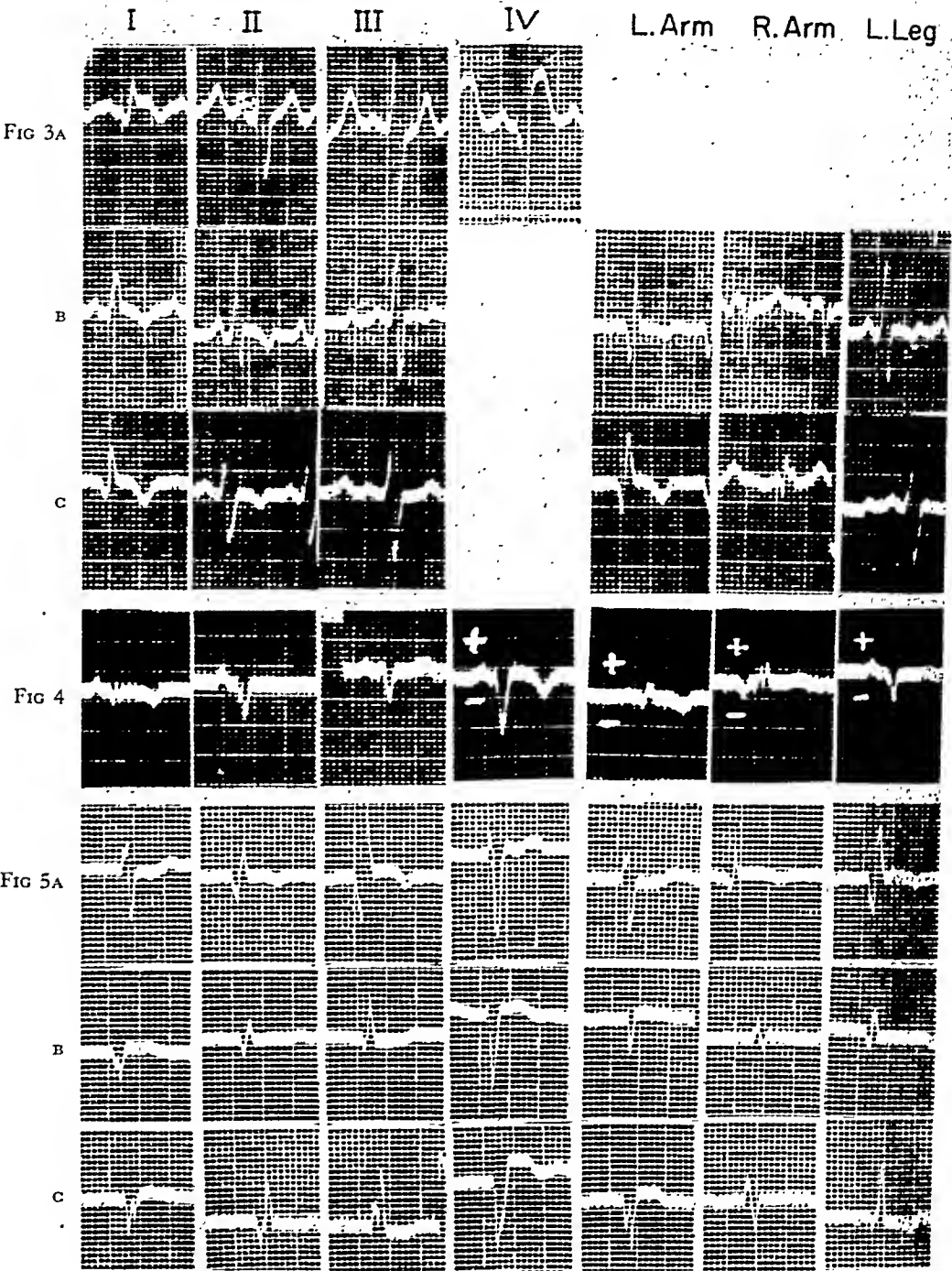


FIG. 3. A patient in whom the $r_1S_{2,3}$ pattern was transient. This patient also did not have an aneurysm. A, taken two days after the patient entered the hospital; B, taken a week later; C, taken two weeks later.

FIG. 4. A case of ventricular aneurysm that shows downward main ventricular deflections in the three standard leads; a fifty-two-year old man.

FIG. 5. Additional cases of ventricular aneurysm. A, fifty-four-year old man; B, fifty-eight-year old man; C, fifty-four-year old man.

$r_1S_{2,3}$ pattern also may be considered in this category. The mechanisms that produce this pattern in the normal and abnormal heart have been reviewed in a previous publication.⁵ Here again, in cases of myocardial infarction, the presence of this pattern depends on the location of the infarct and the position of the heart. In all these cases, the unusual position of the heart was indicated by the upward QRS complex in the right arm lead.

OTHER PATTERNS

Figures 5A, B and C show three other examples of myocardial infarction with ventricular aneurysm. In these cases, the tracings do not resemble the patterns just described. However, in these cases also, the upward QRS complex of the right arm lead indicates an unusual position of the heart. Figure 5A is very interesting in this connection. The deep wide Q and coved T in the left leg lead and leads II and III indicate the presence of a posterior infarct. The right arm lead shows a QR pattern. This indicates either marked clockwise rotation of the heart around its long axis or backward rotation of the apex. The elevated RS-T segment in the right arm lead, indicates that the right arm lead is also facing the epicardial surface of the infarct. This further suggests the presence of backward rotation of the apex.

Regardless of the location of the infarct and the patterns in the standard leads, the right arm lead in all our cases of ventricular aneurysm showed an upward QRS complex. This suggests the following: While the upward QRS complex in the right arm lead may occur after infarction, with or without an aneurysm, its absence in the right arm lead, after myocardial infarction, tends to rule out an aneurysm.

The authors wish to express their appreciation to Dr. Louis Leiter, Chief of Medical Division, Montefiore Hospital, for his advice and preparation of the manuscript.

CONCLUSIONS

When myocardial infarction occurs the patterns in the standard leads and unipolar extremity leads depend on the location of the infarct and the position of the heart. The presence of a ventricular aneurysm may cause unusual rotation of the heart. When this occurs the standard leads may show an $r_1S_{2,3}$ pattern, or the main ventricular deflections of the three standard leads may point downward. Along with these patterns the QRS complex of the right arm lead tends to be upward instead of downward. However, these patterns may occur in the absence of ventricular aneurysm.

All our cases of ventricular aneurysm showed an upward QRS complex in the right arm lead. This suggests that the absence of this pattern in the right arm lead, in a case of myocardial infarction, indicates that a ventricular aneurysm is absent.

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Cardiovascular Syphilis*

I. OGDEN WOODRUFF, M.D.†

New York, New York

THE last ten or fifteen years have seen a renewal of interest in cardiovascular syphilis, especially in that phase which embraces syphilitic aortitis and its complications. Reemphasis of the tragic potentialities inherent in the lesion, unless inactivated before symptoms have appeared, has stimulated the setting up of numerous studies designed to establish criteria for the detection of syphilitic aortitis while still asymptomatic and presumably before its progressive course has caused serious damage. By possessing the ability to recognize it in the latent or asymptomatic phase, the physician might then through proper treatment check the relentless progress of the lesion before damage to the aortic wall became serious and in many instances before the process involved the heart or impaired its coronary blood supply.

It cannot be emphasized too frequently that for the medical man syphilis of the cardiovascular system far and away outranks in clinical importance all other late manifestations of syphilis, both because of its serious consequences and its frequency. As to its frequency, syphilis of the aorta and its complications comprises 13 to 15 per cent of all cardiac diseases found at autopsy. To quote Stokes in his opening paragraph on cardiovascular syphilis, it is "ubiquitous, insidious, disastrous."

The exact nature of the pathologic process in the arteries is the subject of some dis-

agreement. Saphir and Scott have contended that the primary lesion is an obliterative endarteritis of the vasa vasorum of the adventitia and that the damage to the media (of serious consequence) is secondary because of impaired blood supply. However, there must frequently be an inflammatory lesion in the media, as miliary gummata and spirochetes have been found in the media itself. Also, the so-called Herxheimer reaction is rather of the nature of a reaction in an inflammatory process in the media itself. Whether the infection is brought from adjacent lymph glands through the lymphatics accompanying the vessels supplying the adventitia, or whether the vasa vasorum bring the infection to the media, is not decided. McMean has suggested that intimal infection may even come by way of the blood stream itself. Inflammatory and healing reactions with the development of fibrosis gradually take place and as the various foci spread they tend, through rupturing the elastic fibres of the media, to produce the flabbiness and dilatation of the vessel such as is seen in a well developed case of aortitis at autopsy. Fibrous thickening of the intima also takes place in plaque formations buttressing the weak spots in the media, thus preventing, in many instances, the occurrence of aneurysm.

In smaller arteries the end result of syphilitic arteritis is often the obliteration of their lumen with the effect of thrombus

* From the Social Hygiene Committee, New York Tuberculosis and Health Association, New York, N. Y.

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formation. In certain areas this is likely to produce serious results, for example when those arteries supplying the brain and spinal cord are involved. Cerebral softening or complete transverse myelitis may develop suddenly and such lesions may be completely irreversible, especially when terminal arteries without anastomosing branches are attacked. No part of the organism is immune and syphilitic arteritis may be responsible for such diverse conditions as aneurysm of the renal artery finally requiring nephrectomy, or bleeding from a ruptured artery in the gastric mucosa causing death by exsanguination.

Before concentrating the discussion on syphilis of the aorta and its complications, two other manifestations of cardiovascular syphilis deserve brief comment. Unquestionably, syphilitic myocarditis has been found at autopsy but it probably is so rare as to be of no clinical importance, despite Warthin's contention. Any myocardial pathologic changes present in patients with coronary ostial stenosis and incidental associated coronary arterial sclerosis are not syphilitic but merely the result of insufficient blood supply. On the other hand, gummatous involvement of the myocardium, although uncommon, is not so rare but that the clinician who sees much heart disease meets this condition from time to time. The gummatous infiltration occurs most frequently in the region of the septum. Here it interferes with the conduction mechanism, often producing complete heart block. Consequently, with evidence of pathologic changes in the region of the bundle in a patient with positive serologic findings or other signs indicative of syphilitic infection, gummatous infiltration of the myocardium should be given first rank among the various diagnostic possibilities. With nothing suggestive of the presence of syphilitic infection in the patient, consideration of it as a cause

of disturbance of the conduction mechanism is almost purely academic.

AORTITIS*

General Considerations. Syphilitic arteritis is potentially most dangerous when it occurs in the aorta. It may weaken the aortic wall and produce an aneurysm. It may involve the aortic ring and extend into the valve itself, producing dilatation of the ring and aortic valvular insufficiency with or without cusp damage and distortion. It may involve the mouths of one or both coronary arteries causing stenosis, atresia or displacement of the coronary ostia.

As to its distribution in the aorta the arteritis may be localized and slight or extensive and severe. It is found most often in the aortic arch, especially in the ascending portion, and not infrequently shows a sharp line of demarcation at the beginning of the thoracic aorta. It is unusual for it to extend below the line of attachment of the aortic valve cusps into the sinuses of Valsalva, despite the fact that in these sinuses the vasa vasorum have a richer distribution. It almost never extends into the myocardium itself below the aortic ring. It may be found only in the thoracic aorta or rarely in the abdominal aorta alone. The anomalous location of the coronary ostia—at or distal to the line of the aortic ring—seems chiefly responsible for their involvement. Von Glahn reported that of the nineteen cases he recorded as showing ostial involvement, only one ostium was in its normal position in the sinus of Valsalva.

Sex, Race and Age Incidence. Syphilitic aortitis is much more frequent in men than in women, who comprise only 7 per cent of our series. As to race, the figures reported

* Unless otherwise specified or evidence is presented as to their reference, figures and percentages used throughout the text are based on the findings in forty-one autopsied patients with primary aortitis occurring on the First Medical Service of Bellevue Hospital between 1929 and 1946.

TABLE I

CASES OF, SYMPTOMATIC SYPHILITIC AORTITIS SHOWING DEATHS BY DECADES TABULATED TO SHOW RACIAL DIFFERENCES AND SUBGROUPED PATHOLOGICALLY ON BASIS OF CLINICAL EXPRESSION

Aortitis	A	B*	C	D	E	F	G	H	I	J
	No. of Cases	Per Cent	Death by Decades							Per Cent Dead by Age 50
			20-29	30-39	40-49	50-59	60-69	70-79	80-89	
(All cases).....	41	100	1	7	5	15	12	0	1	32
White.....	29	71	0	3	2	13	10	0	1	18
Negro.....	12	29	1	4	3	2	2	0	0	67
Subgroups										
Aortic Insufficiency.....	7	17	0	2	2	2	1	0	0	57
White.....	3	45	0	1	0	1	1	0	0	33
Negro.....	4	55	0	1	2	1	0	0	0	75
Aneurysm.....	9	22	0	0	1	2	6	0	0	11
White.....	7	77	0	0	0	2	5	0	0	0
Negro.....	2	23	0	0	1	0	1	0	0	50
Aortic Insufficiency and Coronary Ostial Stenosis.....	14	34	0	3	0	8	3	0	0	21
White.....	12	86	0	1	0	8	3	0	0	8
Negro.....	2	14	0	2	0	0	0	0	0	100
Aortic Insufficiency, Aneurysm.....	4	9.7	0	1	1	1	1	0	0	50
White.....	4	0	0	1	1	1	1	0	0	50
Negro.....	0	0	0	0	0	0	0	0	0	0
Aortic Insufficiency, Aneurysm and Coronary Ostial Stenosis.....	7	17	1	1	1	2	1	0	1	43
White.....	3	45	0	0	1	1	0	0	1	33
Negro.....	4	55	1	1	0	1	1	0	0	50

* In column B, per cent for group is that of entire number; in subgroups, per cent opposite White and Negro is the relative per cent of race in each subgroup.

TABLE II
DECADE OF ONSET OF SYMPTOMS

Cases	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Not Recorded
Total (41 cases).....	3	5	6	16	10	0	1	0
White (29 cases).....	1	2	3	14	8	0	1	0
Negro (12 cases).....	2	3	3	2	2	0	0	0

DURATION OF SYMPTOMS

Cases	Less than 1 Mo.	1 Mo. to 6 Mo.	6 Mo. to 1 Yr.	1 Yr. to 2 Yr.	3 Yr. to 5 Yr.	5 Yr. to 10 Yr.	Over 10 Yr.	Not Recorded
Total (41 cases).....	5	7	5	6	9	1	2	6
White (29 cases).....	3	5	4	2	8	1	1	5
Negro (12 cases).....	2	2	1	4	1	0	1	1

in various articles naturally vary considerably, according to the part of the country in which the reporting hospital is located. In our own series, twelve, or approximately 30 per cent, of forty-one cases are in the Negro race. In respect to age, from the viewpoint of clinical expression, aortitis with its complications is a disease of late middle life. In the Bellevue series the bulk of the forty-one autopsied patients in whom aortitis was primary and not an incidental finding died after their fiftieth year. The two accompanying tables show the percentage of disease found at different decades, Table I showing the decade in which the patient died and Table II the decade in which symptoms first appeared, as well as length of course after onset. It will be noticed that the disease gives symptomatic expression earlier in life, and its course is definitely shorter in the Negro race than in the white race, also that it causes death in Negroes at a younger age than in whites.

Case histories were not always taken with sufficient care to make the findings as to duration of symptoms valid but they are in harmony with the general impression. The following percentages are based on the total of thirty-five patients in whom complete records were available: 34 per cent were dead within six months; 48 per cent were dead within one year and 66 per cent were dead within two years.

In our total Bellevue series not only did the bulk of the patients, 68 per cent, die after their fiftieth year but 67 per cent did not show symptoms until that age. Even in our patients with aneurysms 45 per cent lived beyond the age of sixty, which was also the period when the greatest number succumbed, while 70 per cent survived to their fiftieth birthday. Of the Negro group, 67 per cent were dead at the age of fifty and 50 per cent of those died from aneurysms.

As previously noted, syphilitic aortitis

comprises about 13 to 15 per cent of all cases of cardiac disease found at autopsy. Difference of opinion exists as to whether aortitis is on the increase. It is likely that any increase is only apparent, partly because (as Stokes calls it) our heightened "index of suspicion" has enabled us recently to detect more cases and partly because the increase of the average life span in the last quarter of a century has brought to light patients whose asymptomatic expression had been delayed until the sixth or seventh decade. Only recently we saw a woman in her sixty-ninth year with unquestionable syphilitic aortitis (aneurysmal dilatation and a strongly positive serologic reaction) who for the first time was entering the symptomatic phase with anginal attacks.

Time of Onset with Reference to the Chancre. Because of the late age at which symptoms from syphilitic cardiovascular complications appear, most articles on aortitis have classified it as a late manifestation of syphilis and we know that on the average twenty years elapse after the initial lesion before symptoms occur. As to the actual time of the onset of aortitis after development of the chancre, however, there has accumulated through the years a growing body of evidence which indicates that the inflammatory process in the aorta starts not later than a very few months after the appearance of the chancre. On the validity of this evidence there is fairly general agreement. If we accept Stokes's basic conclusions that "vascular distribution of the infecting agent and injury to the blood vessels form the groundwork of the pathology of syphilis," it is not illogical to suspect that invasion of the blood vessels coincides with the time of the widespread systemic distribution of the spirochetes throughout the body. Certainly, we have evidence that syphilitic aortitis and even its complications may be present many years before they manifest themselves symptomatically. Twenty

years ago Warthin reported the presence of extensive infiltration of spirochetes along the vasa vasorum of the aorta in the few patients with early syphilis that he examined postmortem. His work has not been confirmed by other pathologists. In 1915, Albutt reported on two men who died suddenly in their early twenties, showing syphilitic aortitis with occlusion of one coronary ostium at autopsy. Recently in the draft, three subjects with syphilitic aortic insufficiency were found on induction examination but their ages were not stated. Stokes reports a case with definite signs of aortic involvement six months after a chancre and cites a similar case three months following infection. We have seen a patient with well marked asymptomatic aortic dilatation and valvular insufficiency with strongly positive serologic findings three years after an insignificant penile lesion for which no treatment was sought. Shortly prior to that infection, this patient's heart had been pronounced normal and he had been granted a substantial amount of life insurance.

PATHOLOGY OF AORTITIS AND ITS COMPLICATIONS

Aortitis. The gross appearance of the aorta with advanced syphilitic aortitis is typical—a flabby, stretched tube, irregularly puckered and scarred, with crisscross striations giving it a wrinkled “tree bark” appearance longitudinally. The appearance of the classical lesion is distinctive but when it is overlaid by associated atheromatous changes, as so often happens in the age group in which it is seen at autopsy, the picture of the arteriosclerotic change may completely overshadow that of the syphilitic lesion. Under these circumstances only microscopic examination may reveal its presence. In its progress aortitis often damages the wall of the aorta to the extent that it gradually gives way; it frequently

spreads to the aortic valve and damages it to the point that leakage often occurs and it often involves the orifices of the coronary arteries, causing narrowing or even atresia. These various conditions may occur singly or in several combinations, as indicated in Tables I and III.

TABLE III
INCIDENCE OF COMPLICATIONS OF AORTITIS
FOUND AT AUTOPSY

Complication	Total Number	Total Per Cent
Coronary ostial stenosis	21	51
Aortic insufficiency	32	78
Aneurysm	20	49

Aortic Valvulitis. When syphilitic aortitis extends into the aortic valve, invasion of the media at the aortic ring causes rupture of its elastic fibres, thereby widening the commissures and increasing the circumference of the ring to a degree that insufficiency of the valve results. In addition, there is often an infiltration of round cells in the aortic cusps which are first thickened and later, as connective tissue retraction occurs, puckered or shrunk so that they fail to meet adequately in diastole, with a resultant increase in the degree of insufficiency.

*Insufficiency of the Aortic Valve.** Pathologic change in the ring is the most frequent cause of valvular insufficiency, for it can produce leakage independently of invasion of the cusps. The combined result of pathologic change in the ring and cusp is an increase in the actual circumference of the ring with a shortening of the edges of the leaflets. As noted from the clinical viewpoint the lesion never extends below the aortic ring into the myocardium or endocardium, nor does it involve the mitral valve.† Today's

* No attempt has been made to follow the criteria of the American Heart Association in differentiating between aortic valve incompetence and aortic valve insufficiency, inasmuch as the lesions in the valve ring producing leakage are on an organic basis.

† Rare instances of both have been reported.

teaching tends to emphasize the incompatibility of the coexistence of aortic insufficiency and stenosis due to syphilitic valvulitis. The argument for this is based on two points; one is that in syphilitic valvular insufficiency the commissures are widened, thus increasing the circumference of the aortic ring, while in aortic stenosis the cusps are fused at the commissures, thus somewhat narrowing the ring. The second point is that calcium rarely infiltrates the ring or cusps in syphilitic aortitis, so that the latter remain flexible and can lie back along the aortic wall in systole even when they are thickened and distorted, with the consequence that no stenosis of the aortic valve is produced. In aortic stenosis, in addition to the encroachment on the lumen by the fusion of the commissures, the valve is further narrowed through the effect that the infiltrating calcium has upon the flexibility of the cusps, particularly at their bases. This causes a stiffening and rigidity which permits little movement in systole and thus narrows the lumen of the valve. In our series of patients with aortic valvulitis with insufficiency, calcific infiltration of the ring and leaflets was present to a much greater degree than we had anticipated, occurring in 7.3 per cent of the patients. We have to revise our thinking in this matter and to accept as a fact that calcific aortic valvular disease as a pathologic entity can overlie a preceding syphilitic valvulitis and produce stiffening and rigidity of the cusps sufficient to cause actual stenosis of the valve, even when the commissures are widened. In all of these patients the commissures were widened and there was adequate histopathologic evidence of syphilitic aortitis. We found damage to the aortic valve with resultant insufficiency in thirty-two of our forty-one patients (78 per cent). In twenty-eight of these, confirmatory clinical evidence of an aortic diastolic murmur was recorded. The aortic valve

and the orifices of the coronary arteries are so close together that one would expect both to be invaded in many instances. They showed joint involvement in twenty-one of the patients.

Coronary Ostial Stenosis. Damage to the coronary ostia is of frequent occurrence in aortitis. It has been reported as occurring in 14 to 36 per cent of autopsied patients, but most authors have not differentiated between those patients in whom the syphilitic aortitis was symptomatic and those in whom in its latent form it was an incidental finding at autopsy in a patient dying from some other disease. Our cases of incidental aortitis are too few, only eleven, to draw any statistical conclusions but ostial involvement occurred in 27 per cent. On the other hand, in our primary cases of aortitis it was found in 51 per cent and in 39 per cent of the cases both right and left ostia were conjointly involved. The coronary artery almost never is invaded beyond this area and consequently it is misleading to speak, as Stokes does, of "syphilitic coronary sclerosis." There are only one or two cases of syphilitic endarteritis of the coronary arteries reported in the literature. As a matter of fact, in patients with ostial involvement there is usually less sclerosis of arteries distal to the lesion than might be expected in the corresponding age group. When present, its histopathologic picture is that of arteriosclerosis.

Coronary artery thrombosis is rarely found with coronary ostial stenosis and in fact is a rare complication of syphilitic aortitis,* even when it is overlaid with severe arteriosclerosis. Myocardial infarction* (sine thrombosis) has followed ostial closure but is extremely rare.

* There were two patients with coronary thrombosis and one patient with myocardial infarction (sine thrombosis) in the primary group. In the incidental group, in which syphilitic aortitis was latent, there was a patient with coronary thrombosis, myocardial infarction and multiple points of rupture of the heart wall.

In coronary ostial involvement the heart muscle not infrequently presents evidence of myocardial damage, mostly replacement fibrosis. This is no more than is consistent with the diminished cardiac blood supply produced by the ostial constriction and the degree of associated atheromatous changes present in the wall of the artery itself. In only a few of the Bellevue patients were these striking or sufficient to cause thickening of the artery or narrowing of its lumen. It is certainly impossible to allot the responsibility for cardiac damage directly to myocardial syphilis in the presence of the other two operating forces, especially in the absence of any confirmatory histopathologic evidence.

Aneurysm. The incidence of syphilitic aortic aneurysm can be dismissed in a few words. It is much more prevalent among men than women, as is syphilitic cardiovascular disease in general, and it is found especially among men whose occupations involve severe and sustained strain, such as furniture movers and stevedores. It occurred in 49 per cent of our patients.

Aneurysm of the aorta is the term applied to a bulging area of the arterial wall in which the aortitis has so greatly damaged the elastic and muscular coats that they have lost their integrity and have given way under the strain of the pressure of the circulating blood. The continuous pressure of the wall progressively enlarges the sac (sacculated aneurysm). Eventually, as a rule, the intima is broken and the pressure causes the circulating blood to extravasate into and between the various coats, further disrupting them and hastening the rate of enlargement. The fibrinous debris and stasis at the bottom of the sac favor thrombus formation upon which is laid a laminated clot which increases in size, often to the extent that a large portion of the sac is filled with this material. Simultaneously, however, the blood finds other weak spots

in the wall of the sac and tunnels out new areas, so that even though the clot becomes of considerable size and well organized, only rarely through this means is the progressive enlargement of the sac permanently arrested. Sometimes the elastic coat becomes so damaged in the entire circumference of the aorta that by its loss of resiliency a considerable general dilatation of the aorta occurs which may involve a large area or length of the vessel. To this type of aneurysm the name "fusiform" is given. Most aortic aneurysms are in the arch, with the larger percentage in the ascending portion, but they may occur anywhere throughout the length of the aorta. While syphilitic aneurysms may be fusiform or sacculated they are never dissecting. On the other hand, arteriosclerotic aneurysms are characteristically fusiform and only rarely are sacculated. When they assume this form they can be differentiated from those caused by syphilis on occasion only after histologic examination.

CLINICAL ASPECTS OF AORTITIS AND ITS COMPLICATIONS

In considering aortitis clinically, we must constantly remember that syphilitic aortitis is an active, progressive lesion extending over a period of many years. Probably rarely, at its onset, if the invasion is acute, there may be some anginal symptoms, usually vague and fleeting. After that comes a latent period of many years' duration, for *aortitis per se is a symptomless disease*. Symptoms occur only when the damage caused to the openings of the coronary arteries or to the aortic valve is sufficient to impair the cardiac function, or when, from pressure, the wall of the aorta breaks down to the extent that the resulting aneurysm causes damage to other structures in the thorax or to the thoracic cage itself, or on rare occasions dramatically makes its symptomatic stage entrance by rupture.

Here in a nutshell is what makes the prognosis so hopeless in most patients with aortitis once symptoms of cardiac failure occur. The normal blood supply to the heart is obviously diminished and irreversibly so by the narrowing of the coronary orifices. If both ostia are involved, there is little opportunity for the establishment of an adequate collateral circulation through the other avenues of myocardial blood supply. In patients with aortic insufficiency there is obviously a considerable lowering of the diastolic pressure which reduces the volume of blood flow through the coronary arteries, even when the patency of their orifices is unimpaired. This coexists with a gradual increase in the myocardial mass, not infrequently to an enormous degree (*cor bovinum*), so as finally to be out of all proportion to that which even a normal coronary circulation supported by a continuously adequate pressure of blood is adapted.

CORONARY OSTIAL STENOSIS

Symptoms. The presenting symptoms are usually those of slight impairment of the coronary circulation, either angina or dyspnea. We have found dyspnea more frequently, although most reports favor angina. Dyspnea, when paroxysmal, is often nocturnal, commonly awakening the patient from sleep. The intensity of this symptom increases rapidly and it is soon followed by frank failure of the left and right heart in rapid succession.

In ostial stenosis, attacks of angina may be of such frequency and severity as to incapacitate the patient and may persist despite complete bed rest. A syndrome of acute coronary failure occasionally seen in syphilitic aortitis with ostial stenosis is that of sudden fulminating pulmonary edema. One woman who was an inpatient on the First Medical Service of Bellevue Hospital continuously for over two years, not only

had anginal pain so severe as to require repeated nerve block but also had many attacks of sudden and alarming pulmonary edema, to one of which she finally succumbed. Postmortem examination showed aortitis with fusiform aneurysmal dilatation, stenosis of both coronary ostia and aortic valvular insufficiency.

Physical Signs. Coronary ostial stenosis even in its symptomatic stage gives no physical signs. In patients believed to have syphilitic aortitis without aortic valvular insufficiency or hypertension, we may ascribe to coronary ostial stenosis any attacks of paroxysmal dyspnea or angina. Under the same restrictions we may consider it responsible for cardiac failure if the heart shows little or no enlargement and if the signs are suggestive of dilatation rather than hypertrophy. As attacks of angina may have preceded the heart failure, coronary thrombosis with myocardial infarction must be ruled out. In none of our patients was coronary ostial stenosis the only complication of syphilitic aortitis, and consequently the physical signs were simply those of the associated lesions. If in syphilitic aortitis ostial narrowing were present alone and had progressed to the degree of causing symptoms of impairment of the coronary circulation or of heart failure, there would be no physical signs by which it could be distinguished. The only physical signs would be those of the underlying aortitis such as the following: If emphysema is not present, some supracardiac dullness at times may be elicited if moderate dilatation of the arch has occurred. Even without aneurysm, a slight sense of pulsation at times can be felt just at or above the aortic area at the right sternal margin.* The aortic second sound is accentuated and without hypertension it is low pitched. Frequently

* This frequently may be appreciated better by placing the ear over the pulsating area than by the usual manual methods.

it is said to have a typical "tambour" quality but, as a rule, it is not sufficiently characteristic to enable one to detect its peculiar quality, except under especially favorable conditions. Certainly, with co-existent hypertension, as so often happens in syphilitic aortitis, the quality of the aortic second sound is not characteristic. However, in the absence of hypertension or of a mediastinal shift to the right, accentuation of the aortic second sound, especially if its pitch is low, should arouse suspicion of syphilitic aortitis, irrespective of whether the specific tambour quality is recognized.

If the change in lumen is sufficiently abrupt in dilatation of the ascending portion of the aortic arch, a systolic murmur, usually soft, may be present in the right second interspace near the sternum. This murmur is rarely heard over the right carotid artery, as are the harsher murmurs of both aneurysm and aortic stenosis. Fluoroscopic examination may give confirmatory evidence of aortic widening or may show increased amplitude of pulsations in the ascending portion of the arch.

AORTIC INSUFFICIENCY

Symptoms. The initial symptoms, as in coronary ostial stenosis, are those of impairment of the coronary circulation or are suggestive of cardiac embarrassment. Both paroxysmal nocturnal dyspnea and angina can be frequent and severe and as the symptomatic stage progresses symptoms and signs of cardiac failure appear. While at first limited to the left side of the heart, signs of right-sided failure rapidly supervene.

Physical Signs. The physical signs peculiar to the lesions are as follows: The most important sign, without which one may suspect but cannot diagnose aortic insufficiency, is a blowing diastolic murmur. This murmur varies in intensity from a softness too faint to be heard except with the direct ear or diaphragm type of stetho-

scope and then possibly only on full expiration in the upright position, to a harsh, readily audible blow. Its point of maximum intensity is usually in the left third or fourth interspace near the sternal border but it may be heard to the right of the sternum and is more often heard in this area in syphilitic valvular involvement than in aortic insufficiency from other causes. The pitch is usually high. Rarely, the murmur may be heard only near the apex. It may be readily differentiated from the murmur of mitral stenosis by its high pitch and blowing quality, while the latter is a low pitched rumble. With insufficiency of the aortic valve present the dilatation of the aortic arch is likely to be greater and the systolic murmur louder and harsher. The aortic second sound usually remains accentuated but in patients with decided increase in the circumference of the ring and distortion of the valves it diminishes in intensity or becomes inaudible. The pulse assumes a characteristic rapid rise and fall (Corrigan pulse), a "pistol shot" sound is audible in auscultation over the femoral arteries and visible pulsations of the carotid arteries sufficiently great to lift the earlobes in systole are present. A blowing systolic murmur of relative mitral insufficiency is usually present and not infrequently an Austin Flint murmur also. This murmur is heard in late diastole and is located just within the apex. It is of a rumbling or, more rarely, a wavy quality and cannot be differentiated by the quality of its sound from the many variations which occur in the diastolic murmur of mitral stenosis. Its presence was noted in 46 per cent of our patients with aortic insufficiency in whom murmurs were recorded. The heart is enlarged to the left, sometimes to an enormous degree, the apex being thrust downward and laterally from its normal position to the sixth or seventh space. Even in patients with extreme enlargement the

apical impulse is usually fairly well localized, although with much dilatation it may be feeble and ill defined. There also may be some enlargement detected as dullness on percussion to the right of the sternal border. However, dullness is not present over the conus area, nor is a diastolic shock palpable in the left second or third space near the sternum. As bundle branch block rarely exists in syphilitic aortic insufficiency, the pulmonic second sound is practically never accentuated as it is in mitral stenosis. This contrast helps in the differential diagnosis. Extreme cyanosis is rare, even with decided hepatic enlargement, in contrast with the degree commonly found in mitral stenosis and cor pulmonale. Engorgement of the liver is likely to be very painful, probably because its rapid development suddenly distends the capsule. It is often of such intensity that the organ feels too firm for simple passive congestion. Auricular fibrillation occurs only occasionally, in contrast to its frequent occurrence in the hypertensive heart and mitral stenosis. In the latter, if of long standing, regular sinus rhythm is so rare that its presence is suggestive of a complicating subacute bacterial endocarditis.

ANEURYSM

Any discussion of the clinical aspects of aneurysm of the aorta, in as condensed a presentation as this, is immediately hampered by the fact that symptoms and physical signs vary so extraordinarily. Even in aneurysm limited to the arch of the aorta, they depend not only upon which portion of the arch is involved but also upon the direction in which the aneurysm extends and the extent to which it exerts its disastrous compressing effects upon the various structures in the thorax and the bony cage. Therefore, it would seem wise to make no attempt to describe in detail the symptoms and findings at various

sites throughout the aorta, together with their several directions of extension but to emphasize chiefly those "key" findings which should arouse the physician's suspicion of the presence of this serious complication.

Just as aortitis exists without symptoms or signs, aneurysm also may be present in silent form; even when symptomatic, one may be unable to elicit any physical signs and comparison of postmortem with clinical diagnoses emphasizes the large proportion of aneurysms that are first recognized at the postmortem table.

Symptoms of Aneurysm of Aortic Arch. In aneurysms of the ascending portion of the arch the early symptoms may be similar to those of aortitis with coronary ostial narrowing but they differ slightly in detail.

Pain is a frequent complaint but, unlike angina, is usually more steady and pressing and occasionally influenced by posture. When the vertebrae are pressed on or eroded, pain may be felt in the back or radiating around the ribs "girdle" fashion. With this there may be at times a "stitch" on inspiration, leading to an erroneous suspicion of pleurisy. Dyspnea when it appears, unless caused by an associated ostial stenosis, is constant. It may have exacerbations, not infrequently nocturnal, but as these are caused by transient episodes of either bronchospasm or edema of the bronchial mucosa, these paroxysms take on a wheezing or asthmatic character. An additional symptom often is cough which is dry, harassing and aggravated by effort. If narrowing of the bronchus through pressure is sufficient to cause "puddling" of secretion distal to the constriction, it may become productive. Blood-streaked sputum usually indicates erosion of the bronchial mucosa, although infrequently it is a forerunner of a sudden, large, exsanguinating hemorrhage caused by rupture of the aneurysmal sac into the bronchus. When

an aneurysm of the transverse portion of the arch of the aorta produces paralysis of the left recurrent laryngeal nerve, the patient's cough assumes a peculiar "brassy" quality which is pathognomonic. By simply hearing it on entering a ward, the experienced clinician can make an accurate "snap" diagnosis of aneurysm of the transverse portion of the aortic arch. The combination of pain, dyspnea and cough should always arouse suspicion of aneurysm of the arch of the aorta. When aneurysm is present and unrecognized, routine arsenical therapy given because of other indications of syphilis is likely to cause these symptoms to be suddenly aggravated after each intravenous arsphenamine injection.

Physical Findings of Aneurysm of Aortic Arch. The most constant and important abnormality is a greatly accentuated aortic second sound. Its significance is much increased when, in addition, a sense of shock can be felt in diastole in the right second space near the sternum. One should mention that this is a sign which may be missed easily if not looked for. If, in addition, the left brachial pulse (radials are more likely to be aberrant) is smaller than the right, aneurysm of the ascending or transverse portion of the arch is almost sure to exist. With this the systolic blood pressure in the left brachial is relatively lower than compatible with its normal variation (normal average difference 10 mm. of Hg), and in cases where the difference in size between the two pulses is too slight to be detected this difference in systolic pressure is in itself diagnostically significant.

In aneurysm of the ascending portion of the arch a systolic thrill of variable intensity may be felt over the base. As in aortic stenosis it may be palpable at times only with the patient in the prone position with the breath held in forced expiration. Accompanying this thrill there is usually a

harsh systolic murmur over the right carotid.

A diagnostic aid in aneurysm of the transverse arch is "tracheal tug." This is a downward pull of the trachea in systole felt by upward pressure on the lower border of the larynx by the thumb and index finger. It is not to be confused with the pulsations of the thyroid arteries, extending laterally in this region, which frequently are misleading. Examination of the larynx may reveal a partial or complete paralysis of the left vocal cord. Any or all of these signs may be present on physical examination with no other abnormal findings in the chest. On the other hand, there may be decided widening of the manubrial dullness. Pulsation about these areas of dullness more frequently can be seen as a general heave in the area involved than actually felt. Rarely, a presenting rounded bulge with true expansile pulsation is present. This occurs when the aneurysmal sac projecting forward has eroded the sternum and escaped from within the thoracic cavity. The trachea at times is displaced. Suppressed or wheezing breath sounds are heard over one lobe of a lung, usually the left upper lobe, if the aneurysm has compressed and narrowed a large bronchus. Puddling of secretions behind the area of compression may cause inflammatory reaction, pulmonary consolidation and also bronchiectasis.

Roentgenologic Findings of Aneurysm of Aortic Arch. If the aneurysm is relatively small and pointed posteriorly the routine postero-anterior film may show no suggestion of it, as its shadow may be revealed only by a film taken in the left anterior oblique or more rarely in the lateral position. Usually, however, a postero-anterior film reveals a decided extension in the shadow of the arch of the aorta. The shape and position of this shadow, especially if continuous with the silhouette of the aorta, together with the clinical findings, will usually warrant a

diagnosis of aneurysm, especially if the shadow shows a well marked pulsation on fluoroscopy. Occasionally, one can see no pulsation on fluoroscopy, either because of a laminated clot or a mediastinitis.

Aneurysms of the Thoracic and Abdominal Aorta. These deserve a few comments. In the former, pain in the back from pressure on the spine is frequent. Examination may reveal dullness or a sense of pulsation to the left of the spine below the interscapular region. Occasionally an expansile pulsating mass may be present. They frequently rupture into the left pleural cavity. X-ray films may show partial destruction of the lower thoracic vertebrae.

With regard to aneurysms of the abdominal aorta, in the past authorities have stated that they were rarely syphilitic in origin even when sacculated and that they did not occur independently of aneurysmal involvement of the aorta above the diaphragm. Both of these statements have been proved erroneous.

In recent reviews of the literature which have excluded cases reported in the pre-Wassermann era and those in which with a negative serologic reaction the diagnosis (either syphilis or arteriosclerosis) was not supported by histologic evidence, analysis of accepted cases has shown that of all aneurysms of the abdominal aorta 58 per cent are syphilitic in origin and of those located in the upper portion of the vessel 75 per cent are syphilitic in origin. Furthermore, they have been found to exist independently of syphilitic aneurysms of the aorta above the diaphragm.

Those that are syphilitic in origin are more likely to produce symptoms than those on an arteriosclerotic basis. Pain is the most frequent symptom. It is steady, boring, usually in the back and is worse at night. It may be girdle-like and influenced by position. Vague digestive disturbances may be present. Occasionally the

patient is aware of a mass or is shaken by a sense of pulsation.

Examination reveals a pulsating mass. Often it is difficult to determine its expansile quality, or to decide whether pulsation is in the mass itself or whether it is merely transmitted from a normal aorta adjacent to it. If the mass is an aneurysm a bruit can often be heard over it. In many cases a systolic thrill may be felt.

Confirmatory signs may be a difference in size between the femoral pulses if the aneurysm is in the lower abdomen or if one iliac artery is partially blocked by thrombus formation. Blockage of distal arteries by embolus may occur.

Rarely, roentgen films show a wide aortic shadow but often reveal erosion of the anterior portion of the vertebral bodies. Death is often caused by rupture into the peritoneal cavity.

DIAGNOSIS OF AORTITIS AND ITS COMPLICATIONS

Any discussion of the diagnosis of syphilitic aortitis separates itself naturally under two headings: (1) The clinical recognition of the complications of aortitis and their differentiation from various lesions presenting points of similarity clinically. The problems involved are encountered almost wholly after the patient's aortitis in its progress has reached the symptomatic phase. (2) The attempt to recognize the presence of syphilitic aortitis when encountered in the asymptomatic phase and, if possible, before any of its serious complications—coronary ostial stenosis, aortic valvular insufficiency or aneurysm—have occurred.

Before entering into detailed discussion of either of the headings just listed it may not be amiss to warn the practitioner that on the basis of evidence furnished by comparison of clinical diagnoses with the corresponding postmortem findings, the

recognition of syphilitic aortitis, even in its symptomatic stage, appears to be fraught with considerable difficulty. The chief causes of our confusion are: (1) the time of life at which the complications of syphilitic aortitis have progressed to the symptomatic stage is also the period when these same pathologic conditions (aortic aneurysm, aortic valvulitis and coronary artery disease) but with different etiologic bases, enter upon the stage of their clinical expression; (2) irrespective of whether syphilis, arteriosclerosis, etc., is the underlying etiologic factor, there are more points of similarity than difference in their clinical expression; and (3) by the time the symptomatic stage of syphilitic aortitis has been reached, the lesion is often overlaid with extensive arteriosclerotic changes and may be obscured by the pathologic changes and clinical findings of a concomitant hypertension or calcific aortic valvulitis.* The manifestations of arteriosclerosis and hypertension dominate the clinical picture so commonly later in life that when they are associated with syphilitic aortitis, this lesion is so masked that the unalert physician does not even suspect its existence until autopsy reveals its presence. Nevertheless, although frequently masked, there are clues through which syphilitic aortitis in its symptomatic phase may be uncovered. However, these are not in the nature of clearly painted sign posts for the direction of the indifferent medical traveler. For the physician to recognize that one of the complications of syphilitic aortitis is the fundamental lesion in the clinical picture, it is of paramount importance that he be acutely aware that syphilis may be at the back of every cardiovascular disorder under his care. Then, and then only, will he make a serologic test a

routine part of his examination of a patient, be alert to checking fine points of clinical differentiation and finally, seek that corroborative evidence of syphilitic infection which is essential in obscure cases when serologic evidence is lacking.

In weighing evidence the following points may be helpful, especially when cumulative: (1) In cardiovascular disease, as between men and women, syphilis is likely to be an etiologic factor in the proportion of 5:1. Thirty-eight of our forty-one patients were men, a ratio of 13:1. (2) While it rarely produces symptoms before the age of thirty-five, from then on aortitis may be expected to show itself with progressively increasing frequency through the fourth and fifth decades. Age beyond that time is no bar to its occurrence, as attested by one of our autopsied patients who presented symptoms at the age of eighty. (3) Cases of cardiovascular disease in the third and fourth decades, especially those in which cardiac failure exhibits rapid progress, are much more likely to be syphilitic when found in the Negro race. (4) Admission by the patient of the existence of a previous penile sore weighs the scale heavily in favor of syphilis. (5) A positive serologic reaction, especially in the later decades, makes it unlikely that other factors, such as arteriosclerosis or rheumatic fever, are the basic causes of any cardiac clinical picture under consideration.

In cardiovascular syphilis one often fails to obtain a positive serologic reaction. Twenty-five years ago it was positive in only about 60 per cent of the cases reported. More recently this average has risen to 75 per cent, and today one may expect that the greater sensitivity of the tests will show an even larger percentage of positive reactions. In our series the Wassermann test gave a strongly positive reaction, either in blood or spinal fluid, in 85 per cent of our patients in whom the test was recorded

* Rheumatic aortic valvulitis also may obscure the diagnosis, even in the later decades and all pathologists have not accepted calcific aortic valvular disease as an independent pathologic entity.

and a weaker one in 2.4 per cent more.* With a negative reaction to the Wassermann test the employment of the Kline and Kahn tests should be routine because of their greater sensitivity. While less specific, a positive reaction may be accepted as confirmatory evidence of syphilis when obtained in conjunction with a clinical syndrome suspected of being on a syphilitic basis. Failure to obtain a history of a chancre is common. In some series it has been as high as 50 per cent. Adroit questioning may elicit admission of a previous venereal infection and the percentage of patients with neither a positive serologic reaction nor a history of venereal disease is probably not more than 10 per cent. In these patients particularly, corroborative evidence of the presence of syphilis which careful search may reveal is most necessary. This evidence may include signs of previous periostitis, a penile scar, suggestive dermal scars or a small patch of active syphilid. A search should always be made for a perforated nasal septum which is of great significance in the absence of any previous nasal operation.

As approximately one-third of the patients with syphilitic aortitis present signs of early syphilitic involvement of the nervous system, additional evidence on which to base a presumption of a syphilitic element in the cardiovascular picture may be secured through a neurologic examination. The general practitioner should train himself in the routine and technics of a neurologic examination so that he may elicit the abnormal neurologic signs. Among these may be mentioned irregularity, inequality, decided contraction, fixity or sluggish reaction of the pupils. Argyll-Robertson pupil and oculomotor palsies of recent origin are of significance. Changes

in the deep reflexes may be obtained, and if early tabes is present, Achilles tendon and testicular sensitivity may be diminished. If a spinal test is not contraindicated, the spinal fluid may reveal supporting evidence of syphilis, ranging from a slight increase in cells or protein to characteristic changes in the gold curve or strongly positive serologic findings. These may occur with a negative serologic reaction.

DIAGNOSIS OF SYPHILITIC AORTITIS IN ITS SYMPTOMATIC STAGE

In clinical syndromes indicative of aortic aneurysm, aortic valvulitis or impairment of the coronary circulation, we have just discussed those factors and data constituting the indirect evidence in favor of syphilis as the etiologic factor. In addition, there are in the specific syndromes a few points of clinical differentiation of sufficient importance to warrant discussion in detail.

*Narrowing of the Coronary Ostia.** The conditions with which this may be confused are angina pectoris (on the basis of coronary sclerosis); myocardial infarction after coronary thrombosis; early cardiac failure on the basis of hypertension and coronary sclerosis; and pulmonary edema in acute dilatation of the left heart from other causes. As hypertension and enlarged heart are frequently associated conditions, no clean-cut differences are obvious. However, in ostial stenosis, angina is usually more severe and progressive and because of ostial obstruction rather than arterial spasm, it is not so likely to be influenced favorably by nitroglycerin. Occasionally the duration of an anginal attack is so long that it suggests myocardial infarction but there is no temperature, leukocytosis, increased

* As coronary ostial stenosis did not occur in our series independently of either aneurysm or aortic valvular insufficiency, despite its frequency except in the asymptomatic group, this discussion is simply for the purpose of emphasizing the symptoms of impairment of the coronary circulation.

* In four of the seven patients in whom no serologic test was recorded, the patient died the day following admission; one other died four days after admission.

sedimentation rate or characteristic electrocardiographic changes such as one finds in the latter. If the heart is but little enlarged, the blood pressure normal and there is a slight dilatation of the aorta and the aortic second sound accentuated and low pitched, attacks of angina or pulmonary edema are much more likely to be on the basis of syphilitic narrowing of the coronary orifice. In general, the electrocardiograph gives no characteristic changes; there may be some splintering of the ventricular complexes, indicating some myocardial damage, and depressed T waves or a depressed ST segment. Even the electrocardiographic changes in response to the anoxemia test simply indicate impairment of the coronary circulation without regard to underlying pathologic changes.

Insufficiency of the Aortic Valve. When this lesion complicates syphilitic aortitis we have to distinguish it from the following conditions: rheumatic aortic insufficiency with or without stenosis, calcific aortic valvular disease, aortic insufficiency on an arteriosclerotic basis, aortic incompetency in hypertension and, more recently, healed bacterial endocarditis with aortic valvular leakage and progressive cardiac failure.

In the first, there may be a history of rheumatic fever. If not seen in the first bout of heart failure, there may be a history of heart distress and even attacks of repeated failure extending over a period of time much longer than usually compatible with life after failure occurs in the syphilitic heart. Furthermore, compensation may be satisfactorily restored in the intervals between breaks, and cardiac failure may recur only because of some respiratory infection, recurrent rheumatic activity* or because the patient has stopped digitalis. While a mitral diastolic murmur may be present

in both conditions, the other signs suggestive of mitral stenosis usually are present in the rheumatic case, namely, an accentuated pulmonic second sound with a diastolic shock, increased dullness over the conus area, and the characteristic x-ray silhouette. This last will be lacking in the syphilitic heart, as will the esophageal displacement by an enlarged left auricle. Auricular fibrillation, rare in syphilitic heart disease, is common in rheumatic heart disease.

In calcific aortic disease the pulse is usually smaller and rarely Corrigan in type. It rises slowly in systole and may have an anacrotic notch. Often the diastolic murmur is inaudible and, when heard, is usually faint. The second aortic sound is either much diminished in intensity or absent over the area of the right carotid artery. A systolic thrill is usually palpable over the right second interspace near the sternum. It is most readily felt with the patient lying prone and holding his breath in forced expiration. In sacculated aneurysm of the ascending portion of the arch, a thrill may also be present, and the pulse may have an anacrotic notch; but in this condition the aortic sound will be accentuated and probably accompanied by a diastolic shock. When syphilitic aortic insufficiency and calcific aortic disease coexist, a high degree of diagnostic acumen may be necessary to recognize the presence of the syphilitic disease.

If aortic valvular insufficiency is associated with the aneurysm, the aortic second sound may be absent, as in calcific disease if the associated valvular damage is sufficiently great. Usually, evidence of much greater aortic dilatation is present than is found in calcific disease. The diastolic murmur is loud, in contrast to the faint murmur described above, and the pulse is large and suggestively Corrigan in type, despite its atypical systolic phase. When, even without aneurysm, the dilatation of

* In active rheumatic carditis, the erythrocyte sedimentation rate is usually elevated even in the presence of chronic passive congestion.

the vessel in syphilitic aortitis produces a murmur sufficiently rough to resemble that of aortic stenosis, then with aortic valvular insufficiency present, the diastolic murmur is usually correspondingly loud. Furthermore, it is frequently loud to the right of the sternum, which is unusual in other conditions; also, the aortic second sound may be accentuated.

Clinically, incompetence of the aortic valve may be caused by the stretching of the ring by excessively high blood pressure. This could be confused only with slight grades of aortic valvular insufficiency due to syphilis. It is found rarely except when the systolic pressure is above 250. It is usually transitory, disappearing when the blood pressure drops below this point. The pulse is usually not Corrigan in type.

There are other cases which, although they form a small percentage of the total, make an appreciable group combining dilatation of the aorta and aortic valvular insufficiency. Whether or not they all fall into the same category, and whether fundamentally they all have the same pathologic changes is an open question. In all probability, some of them are on an arteriosclerotic basis and some are combined syphilis and arteriosclerosis. Clinically, they present a well marked aortic valvular insufficiency without other valve involvement, and often have considerable fusiform dilatation of the aortic arch. One such group has been described in the last two years, in which there is dilatation of the aortic ring and lesions of the cusps, with histopathologic changes differing from those found in syphilis, and without associated syphilitic aortitis. Clinically, they are extremely difficult to differentiate from those cases of syphilitic aortitis with negative serologic reactions and no venereal history.

Acute bacterial endocarditis, hitherto a fatal disease, is cured now by the use of penicillin. In aortic valvular involvement, if

much damage has occurred, a definite valvular insufficiency takes place. This is on the basis of ulceration of a valve leaflet by the bacterial lesion and leads to clinical manifestations of aortic valvular insufficiency, with a diastolic murmur and Corrigan type of pulse, when considerable damage to the leaflet has occurred. Symptoms of circulatory embarrassment are rapidly progressive, leading to cardiac failure with fatal outcome. Without the history it is practically impossible to distinguish between this and syphilitic aortic insufficiency on examination. However, in patients with valvular damage due to preceding bacterial endocarditis, the diastolic murmur is usually much rougher and lower pitched than one would expect to find in syphilitic aortic insufficiency; and it frequently has the musical quality usually associated with a ruptured cusp. Also, there may be a diastolic thrill, a most unusual finding in syphilitic aortitis. There may or may not be a systolic murmur, because without arteriosclerosis there is little aortic dilatation.

Aneurysm. Occasionally, the shape and location of an aneurysm may be compatible with that of a mediastinal mass such as tumor, Hodgkins' disease or substernal thyroid. (If, on account of suspicion of syphilis, treatment is instituted, Stokes states that pulsation along the border of the shadow may finally appear after the periaortitis is dissipated.) Erosion of the vertebrae from an aneurysm may lead to an erroneous diagnosis of Pott's disease, or a lower thoracic or upper abdominal aneurysm may give symptoms suggestive of abdominal visceral changes. In the absence of radiographic evidence of visceral disease, syphilis, especially neurosyphilis or aneurysm, should always be considered in seeking evidence of some cause operating to produce the patient's symptoms.

A sudden hemorrhage from the mouth, sufficiently large to exsanguinate, almost al-

TABLE IV*
CLINICAL AND PATHOLOGIC DATA OF BELLEVUE SERIES

CASE NUMBER	SYMPHILIS PRIMARY	SYMPHILIS INCIDENTAL	SEX	RACE	AGE	DAYS IN HOSPITAL	P A T H O L O G Y																							ASSOC. PATHOLOGY	BLOOD PRESSURE			
							AORTITIS		ANEURYSM		HEART		AORTIC VALVE		CORON. OST. STENOSIS		ARTERIES LUMEN																	
							Thoracic	Abdominal	Uncomplicated	With Sclerosis	Ascending	Transverse	Descending	Thoracic	Abdominal	Dilated	Hypertrophied	Weight (in grams)	Valvulitis	Widening of Commissures	Invasion of Cusps	Inadequacy of Valve	Sclerosis of Valve	Right	Left	Both	Narrowed	Potent	Sclerosed	Thrombosed	Pneumonia	Tuberculosis	Erosion	
1	+	+	M	W	67	+	SI.		4+									800	+	+	+	+	0	0	0	+							150/80	
2	+	+	M	W	59	10	4+			Top								SI.	NR	+	+	+	+	0	0	0	+							NR
3	+	+	M	W	65	+			+									550	+	+	+	+	+	+	+	+	+	+	+				140/50	
4	+	+	M	W	80	5	Oil.		+	+								NR	+	+	+	+	+	+	+	0	+	+	+				150/50	
5	+	+	M	W	67	+		+	+			2	+					0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+		R 150/58 L 118/38
6	+	+	M	N	33	1												0	0	340	+	+	+	+	0	+	0	+						160/60
7	+	+	F	W	62	1				+								0	0	330	+	0	Calcium	+	0	0	0	+	+	+				120/50
8	+	+	M	W	50	+	DIL		+									800	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NR	
9	+	+	M	W	51	+	Oil.		+									840	+	+	+	+	0	0	0	+							154/42	
10	+	+	M	W	55	+												450	+	+	+	+	+	+	+	+	+	+	+				160/60	
11	+	+	M	W	52	+			+									600	+	+	+	+	+	+	+	+	+	+	+				154/46	
12	+	+	M	Ch-N	43	2	Oil.											790	+	+	+	+	NR	NR	NR	NR	NR	+	+	+				NR
13	+	+	M	W	59	10	Oil.	+	+									450	+	+	+	+	+	+	+	+	+	+	+			+	138/50	
14	+	+	M	W	58	+	Oil.											900	+	+	+	+	0	+	0	+	+			+	+		130/42	
15	+	+	M	W	37	+	Oil.			+	+	Inter-Cardiac						NR	+	+	+	+	0	0	0	+							146/50	
16	+	+	M	W	37	+												750	+	+	+	+	+	+	+	+	+	+	+				130/30	
17	+	+	M	W	50	+			+		+							300	+	0	+	0	+	0	0	0	+						100/50	
18	+	+	M	N	62	+				+								NR	+	+	0	+	+	0	0	+							150/60	
19	+	+	M	N	40	+		+										Normal	350	0	0	0	0	0	0	0	+			+	+		140/78	
20	+	+	M	W	60	+												620	+	+	+	+	+	0	0	0	+	+	+				150/76	
21	+	+	M	W	62	2	+	+										310	0	0	0	0	0	0	0	0	+				+		120/70	
22	+	+	M	W	52	5												NR	0	0	0	0	0	0	0	0	+	0	+				125/80	
23	+	+	M	N	55	1	Oil.		+									NR	+	+	+	+	0	0	0	+							180/58	
24	+	+	M	N	35	+			+									550	+	+	+	+	+	+	+	+	+	+	+				164/84	
25	+	+	M	W	42	8	+	+		+								NR	+	+	+	+	+	+	+	+	+	+	+				130/70	
26	+	+	M	W	66	4	+											800	+	+	+	+	+	+	+	+	+	+	+				NR	
27	+	+	M	W	66	+				+	+							Normal	0	0	0	0	0	0	0	0	+						R 125/80 L 110/60	
28	+	+	M	N	61	+		+	+			+	+					240	0	0	0	0	0	0	0	0	+					+	R 140/102 L 118/82	
29	+	+	M	N	52	+			+		+							880	+	+	+	+	+	+	+	+	+	+	+				140/68	
30	+	+	M	W	60	3	+		+	Sacc.								NR	+	0	+	+	0	0	0	+							144/66	
31	+	+	M	N	44	+	Oil.		+									520	+	+	+	+	No Stenosis	+			+						180/50	
32	+	+	M	N	35	+												1050	+	+	+	+	NR	NR	NR	+							160/0	
33	+	+	M	W	38	+		+										700	+	+	+	+	+	0	0	+							180/50	
34	+	+	F	W	55	+			+									400	+	+	+	+	+	+	+	+	+	+	+				140/70	
35	+	+	M	W	54	+			+									765	+	+	+	+	+	+	+	+	+	+	+				115/80	
36	+	+	M	W	55	+			+	+	+							NR	+	0	+	+	+	+	+	0	+	+					176/80	
37	+	+	M	W	45	+				+								590	+	0	+	+	0	0	0	+							120/40	
38	+	+	M	W	52	1	+		+									NR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	120/60	
39	+	+	M	N	25	+				+								550	+	0	+	+	+	+	+	+	+					+	130/0	
40	+	+	F	N	35	+				+								NR	+	+	NR	+	+	+	+	+	+	+					NR	
41	+	+	M	W	68	+		+	+	+	+							NR	+	0	+	0	0	0	0	+							NR	
42	+	+	M	Ch	61	3	+		+									NR	NR	NR	0	0	0	0	0	0	+						240/110	
43	+	+	M	W	45	+												NR	NR	NR	NR	NR	NR	0	0	+							NR	
44	+	+	M	W	52	4	Oil.		+	+								550	Fusion	0	+	0	0	0	0	+	+	+	+				190/120	
45	+	+	M	W	67	+			+		Fus	+	Sacc.					NR	NR	NR	NR	NR	NR	0	0	0	+	+	+				172/94	
46	+	+	M	N	52	+			+	+								NR	0	0	0	0	0	0	0	+	+	+			+		225/160	
47	+	+	M	W	51	1	+			+								500	0	+	0	+	+	0	0	+							90/70	
48	+	+	M	N	83	2	+			+								500	0	+	0	+	+	+	+	+	+						160/65	
49	+	+	M	W	47	+			+									420	0	0	0	0	0	0	0	0	+	0	+	0			146/92	
50	+	+	M	W	60	+			+	+								260	0	0	0	0	+	+	+	+	+	+	+	+	+	+	164/120	
51	+	+	M	W	62	5	+		+	+								650	0	0	0	0	+	0	0	0	+	+	+	+			NR	
52	+	+	M	N	68	3	Oil.		+									640	+	0	+	0	0	0	0	0	+						150/90	

+ = Adequate period of observation (under Days in Hospital)

C = Complete closure (under Coronary Osteal Stenosis)

D = Denied (under Age When Chancre Appeared)

* Chart by Statistical Service of the New York Tuberculosis and Health Association.

TABLE IV* (Continued)

MUR- MURS	SEROL- OGY		TREATMENT	AGE WHEN CHANCERE APPEARED	CAUSE OF DEATH				MICROSCOPIC EVIDENCE	DIAG. MADE CLINICALLY	DURATION OF SYMPTOMS	INITIAL SYMPTOM			REMARKS	
	Aortic Systolic	Aortic Diastolic			Austin Flint	Positive	Negative	Not Recorded				Heart Failure	Pneumonia	Myocardial Infarction		Rupture
+	+	+	4+	0	NR	+				+	+	4 yrs			Cardiac	Aortic Cusps Calcified Sudden Death in Sleep.
NR	NR	NR		+	0	D			+	+	1 wk				Hemoptysis	Right Coronary Ostium Pinpoint
NR	NR	NR	4+	+	25	+			+	+	4 yrs.	+	+	+	PND	Diagnosis made by House Staff
+	+	+	4+	NR	NR			+	+	+	NR				NR	Aneurysm behind Cusp
+	+	0	4+	+	47			+	+	+	3 wks				Noarseness	Myocardial Infarction
NR	NR	NR		+	0	0			0	+	1 wk.		+			
NR	NR	NR		+	0	NR	+		+	0	NR				NR	Calcific Aortic Disease.
+	+	+	4+	0	0	+			0	+	4 mos				Pain in Back	Aneurysm Circ. 10 cm
+	+	0	+	0	D	+			0	+	9 mos.	+	+			Patent Foramen Ovale
0	+	0	4+	0	20	+			0	+	2 yrs	+				
+	+	+	4+	0	D	+			+	+	7 wks				NR	Occlusion of Rt Innominate
+	+	+	A/C	0	0	+			+	+	3 wks	+				Artery by Mural Thrombus.
+	+	+	4+	0	40	+			0	+	2 wks	+	+			CNS Lues - Clinically
+	+	0	4+	+	24	+			0	+	3 yrs	+				Saccular Aneurysm of Splenic
+	+	0	4+	+	22				+	+	14 wks	+				Artery with Calcification
+	+	0	+	+	26	+			+	+	5 yrs				NR	Diagnosis made by 2 Attendings Hydranephrosis
+	+	0	4+	+	0	+			+	+	7 mos.	+	+		Cough	Aortic Valve Calcified Sp Fl Wassermann Neg.
+	+	+	4+	+	D			+	+	+	11 mos	+	+			Ring narrowed Commisures fused
+	0	0	4+	+	25	+		+	+	+	5 mos	+			Cough	Tracheo compressed
+	0	0	4+	0	D	+			+	+	4 mos	+	+	+		Myocardial Infarction Sine Thrombosis
0	0	0	4+	0	D	+			+	+	5 yrs		+			Rupture of Aneurysm into Left Main Branchus
+	+	0		NR	Pos. Sero	+	+		+	+	5 yrs.	+				Erosion of Vertebra and Ribs
+	+	0	+	NR	NR	+			+	+	4 mos	+				
+	+	0	4+	NR	?	+	+		+	+	10 yrs	+			Palpitation	S.B.E. Aortic and Mitral Valves
+	+	+	4+	+	14	+			+	0	NR				NR	Compression of Pulmonary
+	+	+	+	+	NR	+			+	+	NR				NR	Artery by Aneurysm
0	0	0	4+	0	32	+			+	+	4 mos.	+			Chest Pain	Gouger's Disease
0	0	0	+	0	0				0	+	1 yr.	+			Noarseness	Paralysis Left Vocal Cord
0	+	0	+	0	0	+			+	+	NR				NR	Erosion T11,12, L1,2
+	+	+	4+	+	0	+			+	+	4 yrs.	+				Erosion of Manubrium. Aortic Stenosis and
+	+	+	4+	+	19	+			+	+	2 yrs.	+	+			Calcification Pulmonary Infarction
+	+	0	4+	+	0	+			+	+	1 yr				PNO	
+	+	+	4+	+	0	+			+	+	11 yrs	+	+			Right Coronary Cusp Torn
0	+	0	+	NR	NR	+			0	+	NR				NR	
0	+	0	4+	0	19	+			+	+	6 mos	+	+			CNS Lues - Sp Fl Wassermann 4+
+	+	0	4+	+	NR	+		+	+	+	3 yrs				Chest Pain	Cusp thickened and calcified.
+	+	+	4+	0	0	+			+	+	5 mos	+	+			Myocardial Infarction due to Coronary Thrombosis
0	+	0	+	+	32	+			0	+	8 yrs.					Sp Fl Wassermann 4+
+	+	0	+	+	NR	+			+	+	1 yr.				NR	Ruptured Cusp
+	+	0	4+	NR	NR	+			+	+	3 yrs					
0	0	0	4+	+	D				0	+	2 yrs.	+	+			Compression of Left Main Bronchus. Compression
0	0	0	+	NR	NR				+	0	None					of Oesophagus Sp Fl Wassermann Neg
0	0	0	+	NR	NR				+	0	None					Adenocarcinoma of Kidney
0	0	0	+	NR	NR				+	0	NR				NR	Hadgkin's Disease
0	0	0	+	0	0				+	0	None					Active Rheumatic Valvulitis
0	0	0	+	NR	NR				+	0	None					Fusion of Commissures
0	0	0	+	NR	NR				0							Suppurative Pylonephritis.
0	0	0	+	NR	NR	+			0							Multiple small Aneurysms
+	0	0	4+	NR	0	+			0							Miliary Tbc. Cancer of Prostate
0	0	0	4+	NR	0	+			+	0	None					Labar Pneumonia
0	0	0	4+	0	0	+			+	0	None					Pneumonia
0	0	0	4+	0	0	+			+	0	None					Gonuloma of Lymph Nodes,
0	0	0	4+	0	0	+			+	0	None					Pneumonia
0	0	0	+	0	0	+			+	0	None					Pneumonia
0	0	0	+	0	0	+			+	0	None					Thrombosis of Both Coronaries
0	0	0	+	0	0	+			+	0	3 yrs	+				Rupture of Ventricle
									+	0						Pulmonary Infarction

+ = Adequate period of observation (under Days in Hospital)

C = Complete closure (under Coronary Osteal Stenosis)

D = Denied (under Age When Chancre Appeared)

* Chart by Statistical Service of the New York Tuberculosis and Health Association.

ways comes from aneurysmal rupture. In tuberculosis of the lungs and in gastric lesions a single bleeding is seldom large enough to be fatal. Even esophageal varices seldom cause death at their first rupture.

Rarely, one has to differentiate between aneurysm and syphilitic bronchial stenosis. If stenosis occurs in the bronchus on the left side, diagnosis may be very difficult, as the left upper lobe is the site of the so-called "aneurysmal phthisis" described in the medical books of half a century ago and caused by bronchial compression by aneurysm. However, if there is no pulsation or decidedly accentuated aortic second sound, it is not likely that the collapse of the lung is on the basis of aortic aneurysm. Syphilitic bronchial stenosis, causing atelectasis in the right lung, has sometimes been confused because the traction of the right lung uncovers the aortic valve region, making the second aortic sound much more intense. Here again, pulsations are absent, and even if present to a slight extent ought not to confuse us as it is impossible to conceive of an aneurysm without a huge x-ray shadow compressing the right bronchus sufficiently to obstruct it.

Roentgenologic studies may give information in revealing an aneurysmal shadow, the border of which may be seen to pulsate violently on fluoroscopy or by the roentgenkymogram. Esophageal studies may show displacement of this tube by the aneurysm. The bronchoscopist, in our experience, has been more misleading than helpful; pulsations of the bronchial wall have been ascribed to adjacent aneurysm when they were actually due to a tumor mass transmitting a normal aortic pulsation.

Many points stressed in this section may seem ultra-refined or even purely theoretical to many readers. On the contrary, most of them, especially those touching on differential physical diagnosis, are the ones most discussed on ward rounds when problems of cardiac diagnosis are encountered.

In our final classification of these cases as presented in tabulated form we transferred one case from the primary to the incidental group (Case 52). A case of completely uncomplicated aortitis, it could not possibly have caused hypertrophy of the heart to a weight of 640 Gm. Consequently, the syphilitic aortitis is considered incidental here to hypertensive cardiovascular disease. Death occurred from pulmonary edema following pulmonary thrombosis and infarction.

Of the forty-one cases now left and listed in the primary group, the clinical diagnosis was confirmed by autopsy in thirty-seven (90 per cent). Two other cases were correctly diagnosed, one by the house staff and the other by two visiting men, though they were not accepted officially, bringing the total recognized by some member of the staff to 95 per cent.

Aortic valvular insufficiency was present in thirty-one cases and was recognized through its diastolic murmur in twenty-seven of twenty-eight cases recorded. In one case a diastolic murmur was recorded but the pathologist reported no aortic valvular insufficiency.

We did not fare so well with aneurysms which were present in twenty patients. Of these we detected only twelve, confirming the statement that "a large proportion of aneurysms are first recognized at the autopsy table."

While not germane to the subject under discussion, a glance at the listing in the footnote* will reveal what a rich field of study chronic disease offers, and how in even a small group of cases, apart from curiosities and rarities, careful tabulation and analysis may uncover definite evidence, often carelessly overlooked, which will force us to revise our concepts. In the first place, in the symptomatic group coronary thrombosis with myocardial infarction, though

* Unusual or interesting findings revealed at post-mortem in forty-one cases of primary syphilitic aortitis

present in slightly less than 5 per cent of the cases, comes out of the "never" category into which, through our clinical impressions too long unchecked by facts, we have lately been placing it. More important is the discovery that coexistent syphilitic aortic valvular insufficiency and aortic stenosis, which we have long held to be incompatible on theoretical grounds, can and do coexist, as they did to the extent of 12.5 per cent (four cases). One hates to think of the number of generations of medical students to whom each year with increasing fluency due to repetition—and with a slight trace of condescension and superiority—we have proved with the brilliant logic of a medieval churchman what isn't so.*

DIAGNOSIS OF ASYMPTOMATIC SYPHILITIC AORTITIS

A good introduction to the discussion of the diagnosis of syphilitic aortitis in its latent

in the symptomatic stage:

	No. Cases
Right ostial stenosis and myocardial infarction (since thrombosis)	1
Coronary thrombosis with myocardial infarction	2
Calcific aortic valvular disease (aortic stenosis superimposed on syphilitic aortic valvular insufficiency)	4
Calcific aortic valvular disease (aortic stenosis), no syphilitic involvement of valve	1
Ruptured aortic cusps	2
False aneurysm in sac of ascending arch	1
Intracardiac aneurysm	1
Aneurysm compressing left auricle and pulmonary artery	1
Circoid aneurysm of both carotids	1
Aneurysm of splenic artery with calcific infiltration	1
Subacute bacterial-endocarditis engrafted on aortic syphilitic valvulitis	1
Patent foramen ovale	1
Stenosis of mouth of innominate artery by arteriosclerotic plaque causing reduction in size of pulse and blood pressure in right brachial	1
Gaucher's disease	1

* In this pathologic picture, the commissures are widened by the syphilitic process. Then both the ring and cusps are infiltrated with calcium which so stiffens the cusps, especially at their bases or line of attachment to the ring, that the force of the blood against them in systole can raise them but little, with a resultant stenosis of the valve.

or asymptomatic phase, is the admission that irrespective of our diagnostic attainments with syphilitic aortitis in its stage of clinical expression, in the eleven cases in which it was a casual finding at autopsy in patients who were literally sick unto death, we never even suspected its presence. As three of our patients showed strongly positive serologic reactions, we should at least have risked a guess in these cases.

Because in syphilitic aortitis there is a latent or asymptomatic period usually of many years' duration, clinical interest naturally centers around the diagnosis of the lesion in this stage, which has been variously called "early" or "uncomplicated" syphilitic aortitis. However, on recalling the cases cited by Albutt of deaths in the early twenties from syphilitic aortitis complicated by coronary ostial stenosis, one pauses before becoming dogmatic in stating either the decade in life or the number of years after a chancre during which we may presume to find "uncomplicated" aortitis; the best we can do is to try to detect cases of syphilitic aortitis while the disease is still latent (i.e., asymptomatic), and hope that in some of them the process is still "uncomplicated" by coronary ostial stenosis, insufficiency of the aortic valve or aneurysm. Theoretically, the recognition of aortitis in the asymptomatic stage is essential if we are to achieve truly preventive medicine, for by the time patients present symptoms they are *never* in the stage of "uncomplicated" syphilitic aortitis, and furthermore, in the majority of them, because of the inroads the disease has made by this time, their remaining span of life is relatively brief.

This statement is a challenge to the validity of the criteria for the diagnosis of uncomplicated aortitis set up by the United States Public Health Service and a group of co-operating syphilis clinics. These criteria, which were published in 1932 by Cole, were as follows: (1) Teleroentgenographic and

fluoroscopic evidence of aortic dilatation; (2) tympanitic bell-like tambour accentuation of the second aortic sound; (3) a history of circulatory embarrassment; (4) increased retromammary dullness; (5) progressive cardiac failure; (6) substernal pain and (7) paroxysmal dyspnea. In the same article this list is preceded by the statement that "Every effort should be made to recognize the existence of syphilitic cardiovascular involvement while in the stage of uncomplicated syphilitic aortitis, before the development of irreparable anatomic or functional damage to the heart."

Now, every case of narrowing of the coronary ostium is not only a complication of syphilitic aortitis, but a serious complication. Yet, how can patients with syphilitic aortitis, who have no aortic valvulitis or aneurysm, give "a history of circulatory embarrassment"; show "progressive cardiac failure"; have "substernal pain" or "paroxysmal dyspnea" on the basis of a syphilitic process, except through narrowing of one or both coronary ostia? On the other hand, if we are really talking about *uncomplicated* aortitis (i.e., without coronary ostial narrowing, aortic valvulitis or aneurysm), what in the pathology of aortitis *per se* can cause symptoms of impairment of the coronary circulation or of cardiac function? The answer, of course, is nothing.

In progressive narrowing of a coronary ostium, until the volume of blood flowing through the coronary artery is reduced to a point where there is the characteristic electrocardiographic response to an anoxic test, there is no way of determining the presence of ostial stenosis. By that time the initiation of the symptomatic phase is usually imminent. Occasionally, the presence of coronary ostial stenosis is dramatically revealed during a course of antisyphilitic treatment by a "therapeutic reaction" in which edema around the coronary orifices is sufficient to cause temporary closure.

Such accidents have at times terminated fatally.

There is no constant correlation of the degree of narrowing in the ostia with the initiation of symptoms. The rate at which the stenosis proceeds is probably a factor, its slow progress favoring the development of a more or less adequate collateral circulation. The extent of the other sources of myocardial blood supply in all likelihood determines the degree of ostial narrowing for which a collateral circulation can compensate. In cases of death from non-syphilitic causes, atresia of both coronary ostia from syphilitic aortitis, as an incidental finding, has been recorded. Since coronary ostial stenosis cannot be diagnosed prior to the beginning of symptoms, criteria for the detection of uncomplicated aortitis which include symptoms of dysfunction are not only unsound but, by their inclusion of symptoms of impairment of the coronary circulation, are even dangerous, as they fail to warn the general practitioner of the hazards inherent in the treatment of syphilitic aortitis when coronary ostial stenosis is present. Physicians should be taught that paroxysmal dyspnea and angina pectoris are symptoms of impairment of the coronary circulation; so that on meeting them in their patients with apparently uncomplicated syphilitic aortitis, they will realize that they are dealing with a lesion of the coronary arteries in which careless therapy may cause serious and even fatal reactions. The most we can strive for is the detection of syphilitic aortitis in its asymptomatic stage. In any case discovered we can only hope that there has been no invasion of either coronary ostium. There are not many figures available to aid us in determining statistically the likelihood of that hope being realized. Most studies based on necropsy findings have not separated their latent from their symptomatic group. In our Bellevue series the number of cases of asymptomatic

syphilitic aortitis is too small for any general conclusion to be valid. However, coronary ostial involvement occurred in 27 per cent, as compared with over 50 per cent of the symptomatic group. It is interesting to note that in the incidental group uncomplicated aortitis existed in 63.5 per cent of the cases, even though their ages ranged from the fourth through the sixth decades. Also, based on our experience even with the symptomatic group, one may assume that without symptoms of cardiac failure, in aneurysms distal to the ascending portion of the aortic arch, the percentage of cases showing coronary ostial involvement is relatively small. Of these seven cases, in none was ostial stenosis present, and of the remaining thirteen aneurysms of the ascending arch, six showed no ostial stenosis.

In the absence of evidence of aortic valvulitis or aneurysm, what are sound criteria for assuming the presence of latent syphilitic aortitis? In presenting them, we must realize that they are valid only if the patient has not yet reached the end of the fourth decade and shows neither evidence of arteriosclerosis nor hypertension. With these restrictions, we may say that if on auscultation we hear an accentuated aortic second sound of low pitch and of so-called tambour quality, we should suspect syphilitic aortitis. If, in addition, even without definite radiographic evidence of aortic dilatation, the ascending arch in some positions shows exaggerated pulsations on fluoroscopy our suspicion is strengthened; and if also we can hear even a faint systolic murmur in the right second interspace near the sternum, our suspicion increases in geometrical proportion. If dilatation of the arch is undoubtedly present, the diagnosis is almost certain; with a history of syphilis or other supporting physical evidence, such as a positive serologic finding, it is definite. Obviously, we shall detect it in this stage only as an incidental finding during a routine examination and then only if

sufficiently alert to search for it. The evaluation of these different signs and laboratory aids have different weights at different ages of life. In the second and third decades, the quality and accentuation of the second aortic sound has much greater diagnostic significance than later, and if found in conjunction with dilatation of some part of the aortic arch as revealed by a faint basal systolic murmur, it may be considered evidence of syphilitic aortitis, even without a positive serologic reaction. On the other hand, in the later decades, a strongly positive serologic reaction is of especially great weight when the dilatation of the aorta may be caused by either arteriosclerosis or hypertension, which also may obscure or change the quality of the second sound. In seven of the eleven cases in the older age group in which syphilitic aortitis was an incidental finding and was truly "uncomplicated," three showed a strongly positive serologic reaction.

The general practitioner will rarely have much opportunity for detecting aortitis at this stage, though in recent years certain medicosociologic trends have increased the possibilities of early diagnosis through uncovering latent infection. Among these are premarital Wassermann tests, tests in pregnant women and pre-employment medical examinations, many of which include both blood Wassermann tests and chest x-rays. The greatest opportunity today exists in the numerous syphilis clinics throughout the country; but, as at present conducted with insufficient personnel and few skilled internists, there will be relatively few patients in whom this condition will be recognized. That they are probably fairly numerous is shown by the report of McDermott et al. from the Syphilis Clinic at New York Hospital where, over a four and a half-year period, from October, 1936, to April, 1941, syphilitic aortic valvulitis was found in 3.6 per cent of the 2,718 syphilitic patients

examined. The tragic aspect of this report is that of ninety-one of these patients reported on, who did not have aneurysm in addition, 51 per cent had already proceeded to the symptomatic stage. Certainly, in endeavoring to detect more* of these patients in the latent period, greater emphasis should be placed on the importance of every physician including a blood Wassermann test as a part of his general examination of each new patient, irrespective of the condition for which relief is sought. In New York City, where such examination imposes no additional financial burden on the patient, failure to carry out this test is little short of medical negligence. It should be included also, together with a roentgenogram of the chest, as a routine part of a periodic health examination. It is now generally conceded that slight degrees of aortic widening cannot be detected by x-rays. Widening of the ascending portion of the arch may be presumed if that portion of the aorta shows an accentuated curve in the x-ray silhouette. This can best be seen on a film taken in the left eccentric position. With associated hypertension or arteriosclerosis, this dilatation is in no way specific.

In all probability, even if physicians are on the alert to detect the presence of the stigmas of syphilitic disease, the recognition of cardiovascular syphilis at the stage when the disastrous effects of its progress may be prevented is likely to be too difficult to be of practical value on a large scale. Another important factor contributing to the difficulty in recognizing asymptomatic aortitis is the lack of knowledge among many patients of their having had a chancre. Mem-

bers of the low-income groups rarely seek advice except when seriously ill and usually do not come under medical observation until after symptoms begin.

Any hopes for lessening its frequency must rest on: (1) Reduction of the incidence of syphilis through public health measures which at present are grossly inadequate from an epidemiologic point of view and (2) more thorough and efficient treatment of syphilis following its initial appearance and through the secondary stage of the disease. Otherwise, cardiovascular syphilis will continue to be a distinct problem of medicine and an important cause of death.

There is again need of another cooperative study based on the evaluation of diagnostic criteria. At the same time, stricter criteria for pathologic diagnosis are necessary if we are to hope for greater accuracy in correlating clinical pictures with pathologic findings.

Criteria for the diagnosis of uncomplicated aortitis should be dropped, as it is impossible in the asymptomatic stage to rule out some coronary ostial narrowing. The term "uncomplicated" aortitis, if used, should refer in a pathologic classification to those cases without coronary ostial stenosis, aortic valvulitis or aneurysm. In the majority of cases examined at postmortem, the presence of syphilitic aortitis and its complications can be proved without difficulty, and in cases without atherosclerosis an acceptable diagnosis can be made based on the characteristic gross findings in the lesion and in its complications. On occasion, the association of decided atherosclerotic changes in the aorta itself around the coronary ostia or in the aortic valve affecting both the ring and cusps may so confuse the situation that one may not be sure whether the case is a combination of syphilis and atherosclerosis or atherosclerosis alone. Certain criteria should be set up as minimal requirements for classifying as syphilitic cases in which

* One unexpected finding in our Bellevue group was the extraordinarily small percentage of asymptomatic cases. Does this mean that only 20 per cent of the cases of syphilitic aortitis fail to reach the stage of symptomatic expression, or does it mean that pathologists fail to recognize it in many instances when it is an incidental finding? That only eleven cases were recorded in seventeen years would suggest the latter, but the caliber of the work in the Department of Pathology is against it.

atherosclerosis obscures the pathologic picture. However, we should bear in mind that when the type of clinical syndrome strongly suggests syphilis, or when there is a history of or physical evidence for a syphilitic infection, and when the serologic reaction is strongly positive, these factors should be allowed to influence a pathologic decision even if the histopathologic evidence results in the Scotch version "not proven."

In those cases in which the diagnosis is in doubt, sections taken within 1 cm. of the coronary ostia, aneurysm or aortic ring should at least have these minimal findings to permit the classification of the lesion in the ostia, aortic valve or aneurysm, respectively, as syphilitic. Syphilitic ostial stenosis and coronary artery thrombosis rarely coexist; and syphilitic aortic valvulitis rarely invades the leaflets without involving the ring and widening the commissures. Therefore, in the first instance with coronary artery thrombosis present, the section should be taken through the ostium instead of within 1 cm.; and in the second instance, especially if the commissures are described as "fused," sections showing the criteria for syphilis should be required either through the commissural area or leaflet unless, of course, there has been calcific infiltration. These histopathologic criteria, which have been kindly furnished by Drs. Von Glahn and Spain, Director and Associate Pathologist, respectively, of the Department of Pathology at Bellevue Hospital, are as follows:

There should be present a perivascular infiltration of lymphocytes or plasma cells in the adventitia with or without endothelial cell proliferation of the vasa vasorum. The section should show some disruption of elastic tissue fibers in the media, even though minimal, with or without definite stellate vascularized scars. Fibrosis of the intima need not be present to make a definite diagnosis of syphilitic aortitis.

Unless criteria can be established under which no case with bizarre findings can be classified as syphilis except on properly supporting evidence, our statistics will have little meaning, and our actual knowledge of the amount of unusual combinations, such as aortic stenosis and syphilitic valvulitis, and coronary thrombosis and coronary ostial stenosis, will remain purely speculative.

PROGNOSIS OF AORTITIS AND ITS COMPLICATIONS

In considering the outlook for patients with syphilitic cardiovascular disease, there are a number of factors influencing its course and duration. Of these by far the most important is the presence or absence of symptoms. In the asymptomatic stage we have no good yardstick by which we can measure the progress of the disease up to the time we encounter the patient, and consequently we have no estimate of the reserve which may be drawn on before its depletion leads to symptoms of beginning breakdown. As so many patients do not admit having had syphilis, we have little more than an even chance of learning when the syphilitic infection started, and without this we cannot even apply the law of averages to our estimate of the time at which it may show symptomatic expression. On the other hand, in the symptomatic phase we have acquired a fairly accurate estimate of its duration and outcome.

In order to help one another to obtain more knowledge about syphilitic aortitis we must first straighten out our thinking by eliminating meaningless and ambiguous terms we have used loosely and interchangeably in the past. We may properly speak of uncomplicated syphilitic aortitis as an incidental lesion found at autopsy; we cannot use the term as indicative of a pathologic state which has its recognizable clinical syndrome in the living. For, though we may have under consideration a patient in whom

we have detected the existence of even the minimal amount of aortitis that can be discovered by the employment of every modern diagnostic technique, at present we have no means of ascertaining whether the aortitis has invaded the coronary ostia until the patient is practically at the beginning of his symptomatic phase. The term "early" is ambiguous and misleading in that it has often been used interchangeably with "uncomplicated." Furthermore, from the common meaning of the word, it has an underlying implication when used in connection with syphilitic aortitis that there is some correlation between the duration of the disease and its rate of progress. For all we know, a patient with cardiovascular syphilis may carry any one of its complications for many years before symptoms ensue.

In the symptomatic phase of aortitis, prognosis for duration of life is bad. In insufficiency of the aortic valve, death usually occurs within two years from the onset of symptoms and the course is usually shorter when ostial stenosis is associated. In aneurysm the outlook on the average is the same as for these other two conditions, but there is much greater individual variation, as some patients live for from five to ten years after the onset of symptoms; here again, coexistence with either valvulitis or coronary ostial stenosis, or both, hastens the progress. Life is usually much shortened after an aneurysm has caused constriction of the lumen of a bronchus, as pulmonary suppuration soon follows.

Antisyphilitic treatment, if at all effective in the symptomatic group, prolongs life by only a few months when there is coronary artery or aortic valvular involvement. In aneurysm, gains up to two years or more have been recorded in treated cases as compared with untreated groups. The outlook is greatly improved with that group of cases in which, in addition to antisyphilitic treatment, electrocoagulation can be carried

out by wiring in the aneurysmal sac. In cases in which, in addition to wiring, the progress of the syphilitic process has been permanently arrested through effective antisyphilitic treatment, brilliant results have been obtained.

Another important factor which has a great influence upon prognosis is race. (Tables I and II.) The Negro seems to develop symptoms earlier in life and to run a more rapidly progressive course; and he is more likely to show a greater percentage of combined complications. For example, in our Bellevue series, while Negroes comprised 29 per cent of the total cases studied at autopsy, 67 per cent of them showed symptoms before the age of fifty, as compared with 21 per cent in the white group; and 67 per cent died before the age of fifty, as compared with 18 per cent of the white group.

In respect to aneurysm, while Negroes comprised 29 per cent of the Bellevue cases, they accounted for 23 per cent of aneurysms; and while none of the white group having aneurysm died before the age of fifty, 50 per cent of the Negroes succumbed.

Aortic insufficiency was present in 68 per cent of the white patients and in approximately 83 per cent of the colored; 33 per cent of the white cases died before fifty, as compared with 75 per cent of the colored.

The combined lesions of coronary ostial stenosis, aortic insufficiency and aneurysm were present in seven patients; of these, 57 per cent were colored, but this accounted for 33 per cent of the colored group, as compared with 10 per cent of the white group. Only 33 per cent of the white group with this triad of complications showed symptoms or were dead before the age of fifty, while 50 per cent of those in the colored group had become symptomatic by that age, and one had lived beyond the fifty-second year.

In considering the outlook for patients

once their aorta is invaded by the syphilitic process, one speculates as to the percentage in whom the process will remain uncomplicated or at least asymptomatic throughout life. Its frequency as an incidental finding at autopsy might be some clue if we had sound criteria of diagnosis for detecting the syphilitic lesion and were sure that careful search would be made for its presence. It is rather impressive that only eleven cases of incidental asymptomatic syphilitic aortitis were found at autopsy in seventeen years, but even more so that 63 per cent of these were still uncomplicated though in the older age group.

Our knowledge of the variations in the life span of patients with syphilitic aortitis, as measured from the time of the initial infection, is of no value when applied to a patient found in the latent stage. This knowledge is based almost exclusively on studies of patients presenting themselves for treatment because of symptoms. Obviously, in the asymptomatic individual, without evidence of aortic valvulitis or aneurysm, we cannot figure even approximately how many years the patient will live. We can well assume, though, that we can roughly estimate the degree of activity and severity of a syphilitic process by comparison of the amount of damage found with the time during which the process has been operating. Its virulency may be assumed to be in inverse proportion to its duration and proportionate to the degree of damage revealed on examination. This is, of course, without consideration of the malign influences potential in any hidden coronary ostial involvement, a lesion present in a large percentage of cases. Obviously, signs of any involvement of the ascending portion of the aortic arch increases materially the risk of serious developments. Also, when aortic valvular insufficiency is present, even though asymptomatic, the hazard is increased in proportion to the degree of valvular leakage and the amount of

cardiac enlargement present. Even if treated, cardiac failure may ultimately ensue though postponed by the arrest of the syphilitic process. There is always an uncertain and serious potential factor in all cases of syphilitic heart disease, even in the latent stage. Martland reported that of the cases autopsied in his Medical Examiner's Office in which sudden death had occurred, of those in which heart disease was responsible, 33 per cent were due to syphilis. Of these, aortic insufficiency was rated as being most frequently responsible, and aneurysm with rupture of next importance. There is no careful analysis of the degree of coronary ostial stenosis present in those patients with aortic insufficiency who died suddenly. This lesion presents another hazard, which is the possibility that in overzealous treatment for syphilis, it may be responsible for sudden death from heart failure or pulmonary edema.

One aspect of prognosis of which we have little knowledge is the percentage of asymptomatic cases which are likely to remain so or the percentage in which "uncomplicated" aortitis will not progress to the stage of either aneurysm, coronary ostial stenosis or aortic insufficiency. One cannot assume after an analysis of our own fifty-two cases that they are representative of the community in general. The sample is altogether too small. It is interesting to note, however, that of the eleven cases of incidental syphilitic aortitis, seven of them were entirely uncomplicated, and these ranged from the fourth through the seventh decade. Any cooperative study should make this one of its chief interests, and with a re-definition of "uncomplicated" one may hope to get some valuable information.

TREATMENT OF CARDIOVASCULAR SYPHILIS

In planning the treatment of a patient with syphilitic aortitis, we must remember

that we have no way of detecting coronary ostial involvement or the degree of stenosis present in the asymptomatic stage of syphilitic aortitis. Therapeutic reactions in syphilitic involvement of the coronary orifices can produce alarming and even fatal results in rare instances. Consequently, anti-syphilitic treatment of patients with aortitis should be started with caution. In view of the fact that we have seen three cases of serious reactions attributed to bismuth therapy in the last decade,* it is possible that starting treatment with as little as 0.1 Gm. of oil-soluble bismuth may in rare instances be dangerous. This is especially true of patients who already have symptoms of serious heart disease when greater caution in starting treatment must always be observed. This note of warning is sounded because a great deal of oil-soluble bismuth is sold and presumably used by the general practitioner. Incidentally, even doses of 100 mg. do not maintain effective levels given once every five to seven days. In starting treatment with bismuth the physician should remember that water-soluble preparations are absorbed and excreted rapidly. According to Cole, Sollmann and Henderson (1939) injections of water-soluble bismuth such as sodium bismuth tartrate or iodobismutol must be given at least three times a week to maintain a urinary excretion around 2 to 4 mg. of bismuth daily. Oil-soluble preparations such as bismocymol and biliposol should be given twice a week, while the insoluble preparations of bismuth salicylate in oil can be given once a week. One cc. of 10 per cent emulsion of bismuth subsalicylate in oil (125 mg. metallic bismuth) will usually give a daily excretion of from 3 to 4 mg. of bismuth. The absorption of the insoluble preparations is slower than of soluble bismuth, and in

* Two cases cited by Dr. I. Ogden Woodruff. One case cited through courtesy of Dr. Charles Nammack, Director of the Fourth Medical Division, Bellevue Hospital.

starting the treatment of cardiovascular syphilis this is an advantage.

It is advisable to start treatment of all patients with uncomplicated syphilitic aortitis with bismuth rather than the more actively spirocheticidal drugs, such as arsenicals or penicillin. As yet we have too little knowledge regarding the treatment of cardiovascular syphilis with penicillin to discuss it intelligently. Such treatment at present is experimental and must remain so for some time.

In the last few years a fair number of patients considered clinically (without autopsy) to have cardiovascular syphilis have been given, on medical wards, intensive penicillin therapy for acute infectious processes, especially pneumonia, without manifesting any obvious therapeutic reactions. The number coming under the writer's personal observation is too small to permit the drawing of any conclusions, but it does bear out the experience of Evan W. Thomas et al. who at present are employing penicillin in the intensive treatment of syphilitic cardiovascular disease. Here there has been some protection afforded by the employment of bismuth prior to the use of penicillin.

Past experience with bismuth and arsenical drugs indicates that our motto for successful treatment must contain these two apparently incompatible terms: "caution" and "courage"; caution to avoid "therapeutic reactions," and courage to employ arsenical therapy despite its well known dangers. Of late years, most cardiologists have relied more and more on bismuth exclusively for the control of syphilitic aortitis. The syphilologists, however, seem to favor the use of arsenicals as well, and it seems to the author that the weight of evidence is in their favor. The weight of evidence seems to indicate that it is doubtful whether syphilitic aortitis will be permanently arrested unless arsenical therapy is included in any course of thorough

and prolonged treatment. Furthermore, to be effective, arsenical drugs must be given in reasonably adequate dosage. It is wise to start arsenicals cautiously with small doses but, if tolerated well, the dosage should be increased to effective therapeutic levels such as 0.04 Gm. or even 0.06 Gm. of arsenoxide. The arsenical of choice is arsenoxide (mapharsen, chlorarsen or similar preparations) because experience has proved that this is less toxic than any of the other arsenic derivatives now available.

The course of treatment in uncomplicated aortitis should cover at least two years. After any such course of treatment, the patient should be examined every six months with a view to determining either the recurrence of syphilitic activity or any evidence which would suggest further progress in cardiac or vascular damage. Treatment should be initiated with a course of bismuth therapy extending over a period of at least eight or ten weeks. If bismuth salicylate in oil is used, injections can be given every three or four days if the initial doses are less than 0.1 Gm. If well tolerated, however, the dosage should be increased to 0.2 Gm. each week. Following this, arsenoxide should be used, starting with 0.03 Gm. and increasing the dosage to 0.04 Gm. or 0.06 Gm. each week. If lower doses are used, treatment should be given oftener than once a week. Alternate courses of bismuth and arsenoxide over a two-year period are advisable. Each course of bismuth and arsenoxide should extend for a period of from eight to ten weeks.

In the symptomatic phase the same procedure can be carried out, save greater caution needs to be observed, especially when treatment is first started. If cardiac failure is present, compensation should be restored without any antisyphilitic therapy during this period, except the use of iodides. When the patient is no longer in heart failure, bismuth should be started in small

doses and the first course should be extended for at least ten to twelve weeks. Arsenical drugs should be started with great caution, and the patient should be questioned at each visit as to tolerance. Any reactions should be regarded as dangerous and arsenical drugs stopped if they occur. In patients with symptomatic syphilitic heart disease it is always more important to treat the heart disease than the syphilis. No antisyphilitic treatment will repair damaged heart valves or make the coronary ostia more patent once scar tissue has already formed. Cardiac failure is handled as cardiac failure is under all conditions.

Digitalis is indicated, and the patient should be kept on maintenance doses. If any idiosyncrasy seems to be present, better results are sometimes obtained by employing one of the glucosides, such as digitoxin, until cardiac compensation is restored. Bed rest is needed, and during this period of decompensation diminished fluids and a low-salt diet should be routine. As a matter of fact, both of these procedures are necessary even after compensation is established. If decided right-sided failure is present, a mercurial diuretic may be of help and may be given up to two or three times a week. In some cases ammonium chloride in doses of 1 Gm. three times a day may increase the effectiveness of the mercurial. However, we have found that the prolonged use of ammonium chloride is apt to cause gastric disturbance, and consequently we avoid its use when possible. Occasionally cardiac failure expresses itself in the form of an abrupt onset of pulmonary edema. An attack of this nature demands prompt action with bloodless phlebotomy with tourniquet, morphine, oxygen with a pressure mask, aminophyllin and mercurial diuretics. In our own experience since the pressure mask has been available, this procedure is so much more dramatically effective than any of the other measures which

have been used that pulmonary edema will at times rapidly subside by the use of this measure alone. It may be used with oxygen concentrations up to 85 per cent. Attacks of paroxysmal nocturnal dyspnea which come on early in heart failure may be helped by the use of an oxygen mask with about 50 per cent oxygen concentration.

Anginal pain is first to be treated by bed rest. If not sufficiently influenced, nerve block should be our treatment of choice. Neither oxygen nor nitroglycerin is particularly effective in controlling it. Our only other measures are the narcotics, and with their use there is great danger of establishing addiction. A fairly common and annoying complication of nerve block is a neuritis which sometimes lasts for two or three weeks, although usually not for more than a few days. Rarely a pneumothorax is produced during the procedure. For the relief of either pain or dyspnea occurring in aneurysms either eroding bone or compressing the trachea or bronchus, the only humane method is to give sufficiently large doses of narcotics to dull the patient's suffering, irrespective of their constitutional effects.

During the early course of the treatment of either aneurysm or aortic insufficiency in the symptomatic phase, sufficient attention has not been paid to the benefit of bed rest. In the case of aneurysm, a reduction in cardiac rate of 10 beats per minute eliminates over 14,000 beats a day with a proportionate relief of strain on the aneurysmal wall. Similarly, in aortic insufficiency, cardiac failure may be prevented by limiting the work of the heart through bed rest during the first few months of therapy. For example, in ostial stenosis in which the syphilitic activity is in the process of arrest under treatment, permanent cardiac failure may possibly be prevented through bed rest until a greater degree of collateral cardiac circulation for the heart muscle is developed. This is not merely an academic question;

occasionally at autopsy we have seen hearts with almost complete occlusion of both coronary ostia in cases in which, from the history, there had been a fair degree of functional efficiency long after considerable ostial stenosis had been present.

Before leaving the subject of the treatment of aneurysm, one should comment on the improvement in technique which makes highly desirable wiring with electrothermic coagulation of sacculated aneurysms whenever their situation makes them available for surgical approach. Combined with anti-syphilitic therapy, brilliant therapeutic results have been achieved. We should realize that competence in this branch of surgery is rare. In the symptomatic stage of the disease when cardiac failure is present, especially in patients in the lower economic group who cannot protect themselves satisfactorily from severe stress and strain except when in the hospital, the fight is a losing one. Gradually the free intervals between hospitalization become shorter and the period of hospitalization longer, until death supervenes from progressive cardiac failure.

SUMMARY

1. Cardiovascular syphilis is reviewed with especial reference to aortitis and its complications—coronary ostial stenosis, aneurysm and aortic valvular insufficiency.
2. The incidence, pathology, clinical manifestations and differential diagnosis of these complications are discussed in detail, together with prognosis and treatment.
3. In syphilitic aortitis, attention is drawn to the long latent or asymptomatic period and to the attempts to establish criteria for its detection before the appearance of symptoms.
4. The relationship of the complications of syphilitic aortitis to its symptomatic expression, and the prognostic significance of symptoms is discussed.

5. Cases are cited of coexistent pathologic entities usually defined as incompatible or non-occurring, i.e., stenosis of the aortic valve with syphilitic aortic valvular insufficiency, and coronary ostial stenosis with coronary artery thrombosis.

6. Present criteria for the diagnosis of "uncomplicated" aortitis are analyzed.

7. The frequency of coronary ostial stenosis is discussed, with special reference, based on the doctrine of probabilities, to the accepted method of initiating anti-syphilitic therapy in the third stage of the disease.

8. A brief outline of therapy for cardiovascular syphilis is presented.

9. The clinical and pathologic data in fifty-two autopsied cases of syphilitic aortitis from the wards of the Medical Service of the First Division, Bellevue Hospital, are analyzed and cited in connection with various sections of the article.

CONCLUSIONS

1. In its symptomatic phase, syphilitic aortitis can be recognized clinically in a high percentage of the cases seen on an inpatient hospital medical service.

2. The possession of a high "index of suspicion" and the willingness to give careful attention to the finer points of differential diagnosis are prerequisites for its accomplishment.

3. Syphilitic aortic valvular insufficiency and aortic valvular stenosis, when caused by infiltration of calcium, are not incompatible.

4. Asymptomatic aortitis incidentally associated with other diseases requiring hospitalization will seldom be recognized, especially if the aortitis is "uncomplicated." A strongly positive serologic reaction in the upper age group should arouse suspicion of its presence.

5. In syphilitic aortitis, once symptoms of cardiac failure or of impairment of the coronary circulation appear, the outlook is

gloomy, even with adequate treatment, not only for symptoms, but even for any appreciable extension of the life span. Selected cases of aortic aneurysm offer a more favorable prognosis.

6. The immediate outlook for any material reduction in the percentage of cases of syphilitic aortitis which will go on to symptomatic expression is discouraging. The general practitioner will see relatively few cases and will recognize fewer, especially if the prevailing neglect of routine serologic tests continues. So far there is little evidence of any trend toward that integration with the medical services which would ensure examination of patients by men trained in cardiology. Until authorities provide sufficient funds to employ personnel to do a decent epidemiologic job, the incidence of syphilitic infections and of unrecognized and untreated cases will remain high. During this period we may possibly offset the unsatisfactory situation by more extensive employment of rapid penicillin therapy to reduce the duration of infectiousness of syphilis.

7. Uncomplicated syphilitic aortitis is a pathologic entity incapable of producing symptoms; and there are no criteria for its diagnosis which can rule out a moderate degree of ostial stenosis of one or both coronary arteries.

8. Consequently, as uncomplicated syphilitic aortitis has no diagnosable clinical counterpart, criteria for its diagnosis should be discarded and criteria established for the diagnosis of latent (asymptomatic) aortitis without aneurysmal or aortic valvular involvement. This would be of practical importance clinically and would eliminate much present confusion and misunderstanding.

9. Stricter criteria for pathologic diagnosis are also necessary for atypical cases, though they should be sufficiently rigid in all cases to exclude wishful thinking.

10. When these criteria are accepted, a new cooperative study is desirable to correlate clinical and pathologic data on a sound basis. To be of value, the cooperating clinics must have the services of adequately trained cardiologists with in-patient hospital affiliation to insure proper observation of the patient throughout the natural history of his disease from the time of its detection.

11. Because of the unsound criteria established for the diagnosis of "uncomplicated" aortitis, the general practitioner must be re-taught that in syphilitic aortitis, symptoms of impairment of the coronary circulation mean coronary ostial stenosis.

12. Coronary ostial stenosis was present with sufficient frequency in our Bellevue Series to warrant assuming, on a statistical basis, that one is likely to meet it in any case of syphilitic aortitis, especially if the ascending arch or aortic valve is involved.

13. We believe, contrary to most syphilologists, that serious and even fatal Herxheimer reactions have occurred in cases of aortitis with coronary ostial stenosis by the initiation of treatment with the dosages of bismuth at present routinely employed and advocated.

14. The presence of coronary ostial involvement or even stenosis cannot be recognized in the asymptomatic phase.

15. Therefore, in all cases of syphilitic aortitis in which the complication of coronary ostial stenosis *may* be present, we make a plea for the initiation of antisyphilitic therapy with smaller doses of bismuth than at present advocated.

16. From a practical viewpoint, syphilitic aortitis which is *not arrested* is *progressive*.

17. We believe that the activity of syphilitic aortitis cannot be arrested by the use of heavy metals alone.

18. Therefore, with realization of its inherent dangers, we advocate the employment of arsenoxide (or penicillin, after proper experimentation) in the treatment of every case of syphilitic aortitis in which specific contraindications are not present.

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Seminars on Hypertension

Mechanisms of Human Hypertension*

LEWIS DEXTER, M.D.

Boston, Massachusetts

AN ELEVATED blood pressure in man should be looked upon as a physical sign reflecting disordered function of the vascular system. It is comparable with jaundice as related to disease of the biliary system and liver. Hypertension may affect the systolic blood pressure alone, the diastolic pressure predominantly or more commonly both. An elevation of the systolic pressure alone with a normal or decreased diastolic pressure is observed in such conditions as aortic insufficiency, arteriovenous fistulas including patent ductus arteriosus, hyperthyroidism, complete heart block and, most commonly of all, atherosclerosis which is such a common accompaniment of advancing age. The systolic hypertension of atherosclerosis is due to a loss of elasticity of the large arteries. Although atherosclerosis can hardly be considered a normal process, its frequency in patients over fifty or sixty is responsible for the lay belief that normal systolic pressure is equal to 100 plus the age.

There is no unanimity regarding the manner by which diastolic blood pressure becomes elevated in man. Some believe that diastolic hypertension is always of primary renal vascular origin. Proof and disproof of this belief is lacking. Although Castleman and Smithwick¹ have been unable to find any significant renal vascular lesions in biopsy specimens in early hypertension, the objection has been raised justifiably that biopsies contain too little tissue to show representative changes in the vessels of the kidney^{2,3,4} and that physiologic

change may well precede morphologic abnormality.

Many authorities believe that diastolic hypertension is sometimes due to renal disease as in cases of glomerulonephritis, pyelonephritis, the nephrotic syndrome and so forth, but that in most instances it is of extrarenal origin (posterior pituitary, adrenal, central nervous system, unknown factors). Finally, some believe that all diastolic hypertension in man represent a single entity of diverse etiology and that all are mediated through the kidney whether or not renal disease is apparent. It is believed that not only primary renal disease such as glomerulonephritis but also extrarenal factors may act on the kidney to produce elevation of blood pressure. Thus, pheochromocytomas producing adrenalin give rise in certain instances to a sustained non-paroxysmal type of hypertension indistinguishable from that of benign or malignant essential hypertension.^{5,6} Adrenal cortical neoplasms and basophile tumors of the pituitary are usually associated with hypertension. The production of nephrosclerosis and hypertension by the administration of corticoid compounds and sodium chloride to several species of animals by Selye and co-workers⁷⁻¹⁴ has been the most direct experimental attempt to relate the adrenal cortex to hypertension and the kidney. Selye's observations have been confirmed^{15,16} and denied.^{17,18} In man, Perera has shown that the administration of desoxycorticosterone and salt to patients with Addison's disease frequently results in hypertension¹⁹

* From the Medical Clinic, Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

and that their administration to hypertensive patients produces a further rise of blood pressure.²⁰ Neurosurgeons^{21,22} and psychiatrists²³ have suggested that hypertension may be initiated by emotional stress and in time this neurogenic hypertension may produce enough structural change in the renal vasculature to produce hypertension of renal origin. There is no experimental counterpart to this suggestion since neurogenic hypertension in dogs does not produce morphologic changes in the arterioles.^{24,25}

Although there is no unanimity of opinion regarding the fundamental mechanism involved in the elevation of diastolic blood pressure in man, the kidney has been the suspected organ for over one hundred years. Such suspicion was greatly fortified in 1934 by the brilliant investigations of Goldblatt and his associates²⁶ who, for the first time, produced chronic, sustained and readily reproducible hypertension in dogs by partial constriction of the renal artery. Both benign and malignant forms of the disease were produced and these showed striking similarities to the human disease, whereas neurogenic hypertension produced by section of the carotid and aortic sinuses bore little resemblance to human hypertension.²

In man there are innumerable factors which at this stage of our knowledge are not controllable, such as race, sex, heredity, aggravation or masking of the true course of the disease by atherosclerosis, diabetes and the like as well as the difficulty of obtaining interpretable blood pressure readings except by the most meticulous measures.²⁷ At this point little more can be said regarding the nature of human hypertension because developments in this field must await advances in the experimental animal.

An enormous volume of literature has developed in the last decade concerning the mechanism by which the kidney can elevate blood pressure. These studies have been reviewed in detail elsewhere² and only the more pertinent reports will be discussed at this time.

The renin mechanism has received the

most attention by investigators and although its rôle in the production and maintenance of hypertension is still uncertain, its present status will be reviewed. This mechanism consists of: (1) renin, a globulin produced exclusively by the kidney² and is enzymatic in its chemical behavior;^{28,29} (2) hypertensinogen (renin activator, renin substrate) which is probably an alpha globulin³⁰ produced mainly, if not exclusively, by the liver,^{31,32} is normally found in easily demonstrable amounts in serum² and is the substrate on which renin acts to produce (3) hypertensin (angiotonin), a potent pressor and constrictor substance with a molecular weight³³ of about 2700 and (4) hypertensinase which comprises a group of proteins widely distributed throughout the body even in animals who have none of the other components of the renin system.^{34,35} Hypertensinase is enzymatic in nature and destroys hypertensin.³⁴

Renin has been identified in the renal venous blood of dogs with renal hypertension^{36,37,38} and recently it has been shown³⁹ that as blood pressure rises following the application of a Goldblatt clamp to the renal artery of dogs, the renin concentration of systemic blood rises but that despite a persistent elevation of the blood pressure, the renin gradually diminishes until it is no longer detectable. Similar amounts of renin have been detected in the blood of some patients with acute hypertension such as acute glomerulonephritis and toxemia of pregnancy.^{2,40} In chronic hypertension renin has not been detected in the systemic blood.^{2,41} Renin has been found in the renal venous blood of about one-half of a group of hypertensive patients but similar amounts of renin have been found in the renal venous blood in a like proportion of normal individuals.⁴² Using an extremely sensitive method of detection, Taquini and Fasciolo⁴³ have recovered minute amounts of renin from the systemic blood of normal individuals and similar amounts in hypertensive patients. It may be concluded that renin is found in the blood of man and animals during the acute phase of hypertension

but that despite the persistence of an elevated blood pressure, its concentration decreases until it is no longer detectable by current methods of assay.

Although at one time it was reported that in hypertensive dogs and patients the concentration of hypertensinogen in plasma was increased,^{44,45} subsequent studies have failed to reveal any significant deviation from normal values.^{2,46,47}

The concentration of hypertensinase in plasma has been reported to be decreased in acute renal hypertension in animals^{48,49} but this has not been confirmed.² In dogs and in patients with chronic hypertension, normal values have been obtained.^{50,51} Attempts to identify hypertensin in the blood of hypertensive patients and animals have been unsuccessful.^{52,53}

It is seen, therefore, that renin, hypertensinogen and hypertensinase concentrations of plasma are similar in man and in animals in acute and chronic renal hypertension. No consistent abnormality of this system has been found in chronic hypertension although in the acute stages renin has been found to be present in amounts sufficient to account for the observed rise of blood pressure.

Currently there are three possibilities which have been expressed to explain the findings documented above:

1. Renin plays no rôle in the pathogenesis of hypertension of renal origin. Although it has been shown to come into action in peripheral circulatory collapse,^{54,55,56} its effectiveness in combatting shock is slight.^{57,58}

2. Renin may initiate renal hypertension and some other pressor mechanism may take over the function of its maintenance. Ogden and co-workers⁵⁹⁻⁶³ have suggested this as a possibility. They have reported that the sympatholytic agents, yohimbine and F883, produce no fall of blood pressure in animals with early hypertension while in chronic hypertension these drugs produce a fall of blood pressure. On this evidence Ogden and his associates have suggested that the sympathetic nervous system is somehow responsible for the maintenance

of sustained hypertension. It is well known, however, that complete sympathectomy both in animals⁶⁴⁻⁶⁶ and in man⁶⁷ fails to cure long-standing hypertension. It would be of interest to know whether the presence of renin in early hypertension determines the difference in the behavior of these sympatholytic drugs. It has been suggested by Grollman and co-workers⁶⁸ that chronic stages of hypertension are due to a lack of some substance essential for the maintenance of normal blood pressure. They note that the blood pressure of hypertensive rats falls during pregnancy which Page⁶⁹ has recently attributed to an increase in the concentration of plasma hypertensinase in pregnant women. Grollman and co-workers have also reported a greater sensitivity to renin of pregnant than of non-pregnant rats, that unilateral nephrectomy in the rat and rabbit produces in some cases a rise of blood pressure^{70,71} that bilateral nephrectomy in hypertensive rats does not cause the blood pressure to drop to normal levels and that bilateral nephrectomy in normal rats produces a slight rise of blood pressure.⁷⁰ Other investigators, however, have reported that after bilateral nephrectomy in dogs the blood pressure, if elevated, falls to normal⁷²⁻⁷⁴ and if normal, does not rise.^{73,75-79}

3. During the acute phase of hypertension renin may be present in the blood in excessive, easily measurable amounts and during the chronic stage of hypertension the amount of renin necessary to maintain hypertension may be too small to detect by current methods of bio-assay. Wakerlin and Goldblatt have made interesting and pertinent observations in this regard. Abandoning the relatively insensitive methods of bio-assay for renin, Wakerlin and his collaborators⁸⁰ made the important observation that injection of hog renin into a dog produced an antibody (antirenin) not only to the hog renin but also the dog's own renin. They first reported that the blood pressure of hypertensive dogs fell as the antirenin titer became elevated. Subsequently, they observed that an elevated

antirenin titer in the blood did not prevent the development of renal hypertension nor did it necessarily effect a fall of blood pressure in hypertensive dogs. On the other hand, a fall of blood pressure sometimes occurred in hypertensive animals without a significant rise of antirenin titer.^{81,82}

Goldblatt^{83,84} reports that using a more highly purified hog renin and possibly obtaining somewhat higher antirenin titers than Wakerlin, a high antirenin titer not only prevented hypertension by constriction of the renal artery but consistently caused the blood pressure of dogs made hypertensive months or years before to return to entirely normal levels.

There the matter stands at the time of this writing. If a high antirenin titer invariably causes an elevated blood pressure to return to normal, attempts should be made to produce an antibody against human renin, which so far have been unsuccessful. If hypertension can exist in the face of a high antirenin titer, renin is obviously not the cause of renal hypertension and the pathway of future investigations might well follow the leads suggested several years ago by Bing⁸⁵⁻⁸⁷ or be directed toward the VEM as described by Shorr and co-workers⁸⁸⁻⁹⁰ in this series of articles.

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Hepatitis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FRANKLIN M. HANGER: Since this country entered the last World War it has been estimated that over a million Americans have become victims of acute hepatitis. This disease has been so prevalent on our wards that there are probably few of you who do not believe that you are experts in the diagnosis of liver disorders. Therefore, we will not deal with the various clinical manifestations of hepatitis but will stress certain aspects of the subject which are still not well understood and still controversial.

It might be profitable to review briefly with you the changes that occur in the liver during hepatitis. Recent biopsy studies made by a number of observers during the preclinical stage of the disease as well as during the period of jaundice and convalescence have revealed that the lesions do not consist solely of parenchymal destruction, as was formerly believed, but that other structures of the liver are commonly involved. Mallory, in an excellent histologic report of a large number of cases of hepatitis studied in volunteers,* has pointed out that the chief portions of the lobule affected are (1) the polygonal cells forming the liver cords, (2) the reticuloendothelial lining of the sinusoids and (3) the portal and periportal areas at the periphery of the lobules. In most cases of hepatitis all three of these types of lesions are present, involvement of the parenchymal cells, the Kupffer cells and the periportal areas.

Figure 1 is a diagram of the normal human liver which shows in a schematic way where the virus of hepatitis strikes.

* MALLORY, T. B. The pathology of epidemic hepatitis. *J. A. M. A.*, 134: 655, 1947.

First, the cords of the parenchyma become distorted and swollen. The affected cells become eosinophilic, lose their normal granulation and appear as homogeneous red-staining material in which the nucleus becomes fragmented and pyknotic. Later these cells gradually disappear. The extent of the lesions in different cases varies from only a few scattered abnormal cells to entire destruction of the lobule. As parenchymal involvement increases, a corresponding impairment of the various functions of the liver may be demonstrated by standard tests.

The second type of lesion involves the sinusoids. The Kupffer cells which line the spaces through which blood flows between the liver cords are swollen. They become highly proliferative and sometimes the sinusoids are actually blocked by a great number of histiocytes which are assumed to be the result of multiplication of the Kupffer cells. Disturbances of the reticuloendothelial elements may lead to portal hypertension, impairment of the removal of certain substances of the blood and to the elaboration of abnormal serum globulins.

Third, and equally important, are the inflammatory changes in the portal and periportal areas. These portions of the liver become infiltrated chiefly with histiocytes, lymphocytes, a few polymorphonuclears and eosinophiles, with considerable congestion and swelling of the interstitial tissues.

An understanding of the morphologic changes occurring in hepatitis is essential to an understanding of the differences all of you have noticed in the laboratory findings

in individual cases. In rare individual cases we find one element involved almost exclusively, and liver biopsies of such cases give us an explanation of why liver functions may vary in the different types of hepatitis. For instance, when the Kupffer

phosphatase is not significantly elevated. The direct, prompt-reacting bilirubin of the blood tends to be elevated, and various metabolic functions as indicated by cholesterol esters and galactose tolerance show impairment.

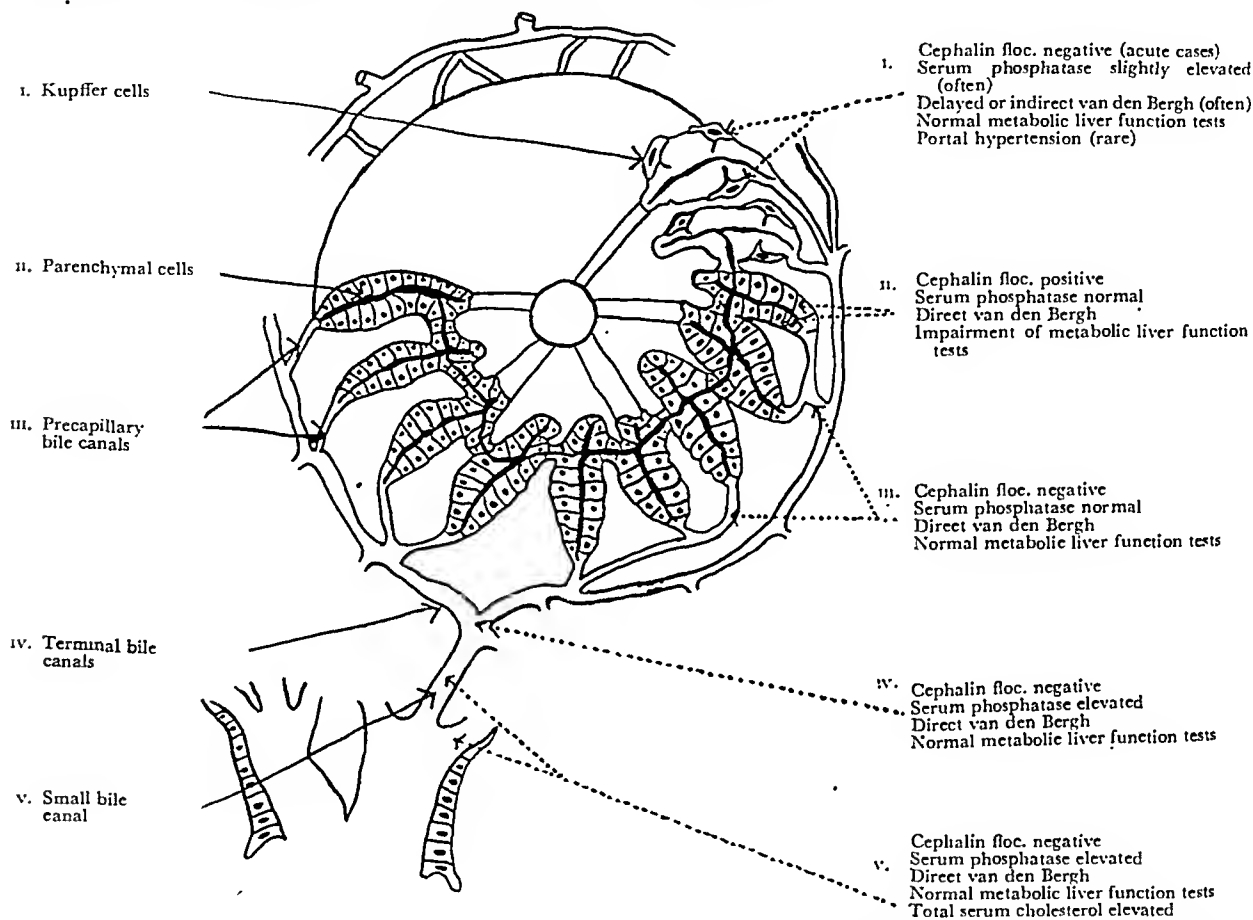


FIG. 1. Diagram of an hepatic unit representing an attempt to correlate the location of the lesion in hepatitis with changes in the laboratory findings. It should be emphasized that the relationships indicated are tentative only since the available data upon which the schema is based are inadequate. Adapted from Lichtman, "Diseases of the Liver." (Redrawn from L. Aschoff, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*).

cells become swollen and inadequate, laboratory studies show a negative cephalin flocculation test, the serum alkaline phosphatase is somewhat elevated and there is an increase in the indirect or delayed-reacting bilirubin of the serum. The metabolic functions of the liver cells, as indicated by cholesterol ester levels, galactose tolerance tests, etc., are relatively unimpaired. There may be enlargement of the spleen, ascites and evidence of portal congestion.

When the parenchymal cells are chiefly involved, the cephalin flocculation and thymol turbidity tests are positive but the

In rare instances of hepatitis the patient is deeply jaundiced and yet the cephalin flocculation test is negative and liver function tests are normal. We have had biopsy studies in three of such patients and in all an intense inflammatory zone surrounding the lobule was the sole lesion. The liver parenchyma appeared normal and the Kupffer cells were not particularly prominent, but areas of free bile accumulating like little puddles could be seen in the inflamed perilobular zone as if there were disruption of small bile canaliculae with extravasation of bile into the tissues.

Patients with this lesion, as I said, give us very little evidence of liver impairment by ordinary tests. The striking feature is a deeply jaundiced person, feeling quite well and with normal liver function tests.

When the portal areas become involved there is more injury to the liver, directly and indirectly, than one would suppose at first glance. It is through this area that the portal blood passes into the lobule and lymphatic drainage takes place. It is also through this area that the smaller bile ducts pass. When the periportal areas become swollen and congested there is frequently pressure on all structures traversing them. Just as injuring the stem may affect the development and quality of a cluster of grapes, so may inflammatory processes in the portal area affect the blood supply and functioning of the hepatic units.

STUDENT: Dr. Hanger, do not these variations in the pattern of liver involvement in hepatitis make it very difficult to establish the diagnosis of hepatitis by laboratory tests?

DR. HANGER: Fortunately from the standpoint of the clinician, cases of hepatitis rarely fail to show some indication of parenchymal damage. Hepatitis of the cholangitic type in patients over forty is particularly disturbing when the laboratory findings point strongly to the jaundice being of the obstructive type. In such instances the disorder should be followed for at least six weeks; if there is no improvement, abdominal exploration is indicated to rule out stone or neoplasm. An operation in such cases is not entirely futile, even when extrahepatic obstruction is not found; for clearing of the jaundice sometimes follows exploration and drainage of the common duct in instances of cholangitis with intrahepatic obstruction. The reason for the beneficial effect of this procedure is not clear.

We must go on now to the question of the etiology of hepatitis. Dr. Neeffe, of the University of Pennsylvania, an investigator who has contributed a great deal to our understanding of the agents causing the

disease, is with us this morning and we have asked him to tell us about his work.

DR. JOHN R. NEEFFE: It might be well to review rather briefly the known facts about the etiology of this disease or perhaps we should say family of diseases.

I would like to emphasize that many of the comments that I shall make today are the result of the pooled observations of many workers and, while some of the observations refer to work done at the University of Pennsylvania in conjunction with Dr. Joseph Stokes, Jr., Dr. John Reinhold, Dr. Sydney Gellis and others, they often were preceded, obtained independently, or else confirmed by the observations of other workers, including Havens, Paul, Oliphant, Cameron, Voegt, MacCallum, Findlay, and a number of other workers in England.

The etiologic agents involved in the problem of viral hepatitis have many properties which justify their tentative classification as viruses even though, as you all know, they have not been isolated or visualized and the evidence, therefore, is indirect. From the literature, one can garner quite a number of observations which give us some idea about these properties, and while they may not hold for all the strains of virus concerned—actually we do not know how many are involved—they do illustrate their probable general characteristics. We know that the etiologic agent of viral hepatitis passes through bacteria-retaining filters. We know it survives heating for at least an hour at 56°C. More recently, however, it has been shown that at least one of these strains of virus is inactivated, under certain conditions, by heating at 60°C. for a period of ten hours. This was under special experimental conditions and whether a shorter period of heating or a lower temperature would have been adequate is not yet known. However, there is this evidence that the virus can be destroyed by heating and fortunately such treatment can be applied to certain preparations, such as human serum albumin, which are now coming into more widespread use. Un-

fortunately, this treatment cannot be applied to whole blood, plasma or serum because, apparently, denaturation or coagulation of other proteins occurs. Oliphant has obtained some evidence to suggest that the viruses in plasma may be inactivated by exposure of the plasma to ultraviolet light. These data are not conclusive and as yet we do not know whether this affords a practical and effective means of treatment of blood products that is adaptable to large scale application.

We know that this virus (or group of viruses) survives for long periods under rather diverse conditions: tropical conditions, arctic conditions, and for long periods of time in our laboratories at room temperature. They survive in the presence of concentrations of certain disinfectants which apparently are adequate to control bacteria, for example, merthiolate, equal parts of phenol and ether, and others. These observations are important because they indicate the sturdiness of these agents and account for many of the problems that arise in their control.

No consistent or reproducible lesions have been observed in chick embryos that have been inoculated with infectious material and definite evidence of propagation of these viruses in tissue culture has not been obtained. No inclusion bodies have been found in the pathologic studies on material from patients with hepatitis. The most serious problem, from the viewpoint of investigation, has been the failure to find a susceptible laboratory animal, which, as you all know, is the reason why the use of human volunteers has been necessary for most of the studies to date.

We were fortunate during the early stages of our work to obtain materials that appeared to contain viruses that apparently caused somewhat different types of hepatitis under somewhat different conditions. It now seems that these two strains of viruses, the exact relationship between which is not known, are responsible for the two similar forms of hepatitis that we now recognize clinically, namely, so-called *infectious* or

epidemic hepatitis and so-called *homologous serum hepatitis*. For convenience in reference, we have called the one strain, obtained from persons with infectious hepatitis, *Virus IH*, and the other has been referred to as *Virus SH*. The behavior of these two strains of virus in human volunteers differed consistently. For example, there was a rather characteristic difference in respect to the type of onset of the disease in these experimental cases. However, from the literature and clinical observations it appears that the more abrupt onset and the more frequent occurrence of fever of significant degree with the onset of infectious (virus IH) hepatitis, as observed in the experimental cases, are not sufficiently consistent to serve as a means of differentiation between the two types of hepatitis. Yet experimentally it was a rather consistent difference.

Also consistent was the difference in interval from inoculation to the onset of hepatitis and this was true regardless of the route of entry of the virus. Thus, regardless of whether virus IH was given orally or parenterally, the incubation period was the same, that is, between eighteen and thirty-seven days. However, when virus SH was injected parenterally, a period of two to five months consistently elapsed before the onset of the recognizable disease. It was of interest that when this virus (SH) was given parenterally, the incidence of hepatitis in volunteers was very high, approximately 75 per cent. However, when it was given orally, neither in our series nor in that of Dr. Havens at New Haven did recognizable hepatitis result. When virus IH was given orally, the incidence of virus hepatitis was very high, approximately 80 per cent. In Dr. Havens' volunteers, the incidence with this type of virus (IH) was about the same regardless of whether it was given orally or parenterally. With our strain of virus IH the incidence in normal volunteers after parenteral injection was rather low but it was capable of inducing the disease by this route. These observations demonstrate a point that I desire to emphasize, namely,

that homologous serum hepatitis actually is not a single etiologic entity. It is a syndrome that may be the result of either one of these two strains of virus and therefore we must recognize at least two syndromes when we face clinically the problem of so-called homologous serum hepatitis. In the one the onset occurs two to six weeks after entry of the virus (IH), and with the other the onset occurs two to six months after entry (virus SH type).

Another interesting difference experimentally is the fact that virus IH usually is present in the feces of patients during the active disease. I might point out at this time that it is not yet known how long the virus persists in the feces and therefore it is not possible to give an accurate estimate as to how long it is necessary to maintain infectious precautions. Interestingly, it has not yet been possible to demonstrate virus SH in the feces of patients with this disease. However, these experiments are incomplete in that most of the virus SH preparations were administered orally. As plasma known to contain virus SH and to produce the disease when given parenterally has failed to induce recognizable hepatitis when given orally, the absence of positive disease on oral administration does not conclusively show that feces do not contain the virus. This may only mean that this virus is not very effective when it enters by any route other than the parenteral one.

The studies on immunity were perhaps most significant in demonstrating the existence of an actual difference, at least antigenically, between these two strains of virus. Volunteers who had virus SH hepatitis and after recovery were reinoculated with the same strain of virus were resistant to reinfection up to at least one year, the longest period of time after which the presence of homologous immunity was tested in our series. However, these same volunteers who were resistant to reinfection with virus SH were not resistant to virus IH, developing the typical disease when inoculated with this virus. The experiment could be reversed and run in the opposite

direction; volunteers who had had virus IH hepatitis and had been shown to be resistant to reinfection with this virus developed typical disease two to four and one-half months after inoculation with virus SH.

It is interesting that during the two- to four-month interval between inoculation with virus SH and the onset of the recognizable acute hepatitis some of the volunteers had several periods of transient minor symptoms. These were not very significant clinically, consisting merely of a day or so of malaise and mild symptoms. In some these periods were associated with slightly abnormal results of certain hepatic tests. Of great importance is the fact that blood taken from such volunteers during these (and even completely asymptomatic) periods has been shown to contain the virus. These observations suggest that, although there is this long interval, there may be some activity of the disease during the long interval. The occurrence of viremia in the absence of significant clinical symptoms and before the onset of acute hepatitis is one of the serious problems contributing to the difficulties in control of the disease and indicates the probable relative ineffectiveness of exclusion of blood donors with a history of overt hepatitis as an adequate means of prevention.

I think then, on the basis of the evidence available, we can say that the existence of at least two somewhat different strains of hepatitis viruses has been adequately demonstrated and, although the possibility of existence of other strains remains, our approach to the viral hepatitis problem, for the time being, has to be centered about the existing knowledge concerning the two recognized strains.

I think it is fairly obvious from the discussion thus far that, experimentally at least, there is evidence of homologous immunity following an infection with either of these viruses but that effective cross immunity does not occur. These experimental data are supported by clinical and epidemiologic observations. Thus it was observed during the war by Dr. Gauld and

others that persons who had so-called yellow fever vaccine or post-vaccinal hepatitis were, if anything, more susceptible at a later date to epidemic hepatitis than were those who had not had the post-vaccinal disease. Likewise, persons who had had "catarrhal jaundice" or sporadic hepatitis prior to military service developed post-vaccinal hepatitis with the same frequency as those who had not.

With respect to the question of second attacks, we have all seen patients who tell us that they have had hepatitis or jaundice two or three times, separated by long asymptomatic intervals. It often has seemed reasonable to assume that these represented second attacks of the same disease. A history of two attacks of hepatitis is obtained in approximately 2 to 5 per cent of patients with jaundice. However, in view of what we now know, we cannot assume that these second attacks necessarily were due to the same virus or that they necessarily constitute evidence against the existence of prolonged homologous immunity following an attack of viral hepatitis. For example, I recently have seen a patient who had virus IH hepatitis in 1944 and in 1947 a second attack of jaundice that clearly was associated with infectious mononucleosis.

Some interesting theoretical possibilities in regard to immunity are suggested by the studies on gamma globulin as used in attempts to protect passively against these two diseases. I think it is fair to say at the present time that most of the workers in this field accept the evidence that gamma globulin is an effective prophylactic agent against the epidemic or virus IH type of hepatitis. If it is given to exposed persons during the incubation period prior to the onset of symptoms, a very marked decrease in the incidence of the disease in those receiving gamma globulin has been noted under epidemic conditions.

In relation to serum hepatitis the results with gamma globulin have been confusing and difficult to interpret. Experimentally, when plasma containing virus SH was mixed with gamma globulin, as in a neu-

tralization test, and the mixture injected into volunteers, the incidence of the disease was not reduced nor was the course of the disease obviously modified. Thus the gamma globulin used either did not contain protective substances effective against virus SH under the conditions of the experiment, or if present, they were not present in sufficient concentration to protect. Likewise, when virus SH was injected parenterally at the same time gamma globulin was injected at a different site, the incidence of hepatitis was the same as in the group of volunteers who received only virus SH.

There are some data on this point from studies in Army hospitals where battle casualties who had been given transfusions later received gamma globulin. There were two such studies. In one study by Duncan and his associates, battle casualties received one dose of gamma globulin on admission to an army general hospital. The patients all had a history of blood or plasma transfusions during the preceding several months. No effect on the incidence of serum hepatitis was detected in this group. However, in another similar study by Grossman, Stewart and Stokes, two doses of globulin were given at intervals of one month. In this series, the data indicated a decrease in incidence as compared with that in battle casualties who had been given transfusions and who did not receive gamma globulin. These observations, however, plus the experimental data cited, indicate that gamma globulin has not yet been proved conclusively to be an effective means of prophylaxis against serum hepatitis (virus SH type) and I think sufficient work has been done to say that it does not seem to afford the same protective effect against the virus SH type of hepatitis that it does against the epidemic virus IH type.

This suggests several theoretic possibilities concerning the extent of the natural distribution of these two types of hepatitis virus. Gamma globulin is prepared from large pools of human adult plasma. If we assume, on the basis of the studies mentioned, that there is a reasonable quantity

of "protective substances" in gamma globulin effective against virus IH, it seems fair to assume that many adults have been exposed to this disease at some time in their lives. On the same basis, it seems possible that relatively few persons, at least prior to the introduction of the large scale use of blood and its products, had been exposed to the SH type virus. This seems reasonable in view of our present knowledge concerning the two viruses, namely, the fact that virus SH does not seem to be very effective in inducing overt hepatitis when it enters by any other route than by the parenteral route. These various observations suggest that the IH strain of virus may have been much more widely distributed in the general population than was the virus SH strain. It is interesting then, if this is the case, that most of the large hepatitis outbreaks resulting from injections of blood or its products, or of biologicals containing blood products, have been of the virus SH type. One would expect, on the basis of the suggested frequency of distribution, that the virus IH type of hepatitis in relation to transmission by blood or its products would be more frequent than the virus SH type. It seems to me that this possibly could be explained by the inclusion in large plasma pools of sufficient "protective substance" from the plasma of immune adults to neutralize any IH type virus that also might be included; whereas, if few adults have "protective substances" effective against virus SH, any virus of this type that is present would not be neutralized. I wish to emphasize that this is purely a theoretical explanation and that there is no factual basis for it as yet except that it does seem to be in accord with some of the known indirect facts. If true, we possibly should expect to find most of the cases of serum hepatitis due to virus IH (short incubation period) occurring in relation to the use of whole blood.

It seems important, therefore, to get away from the concept of the syndrome of homologous serum hepatitis as a single etiologic type, namely, the long interval

(virus SH) type. The syndrome actually is composed of at least two forms of hepatitis, one (virus IH type) occurring two to six weeks after injection of a blood product and the classical (virus SH) type occurring after two to six months.

What are the various ways in which such viruses can be acquired? When one considers the many opportunities for entry of a virus by the parenteral route inherent in modern methods of medical practice, the extent of the problems created by the changes that appear necessary for prevention becomes alarming. Opportunities for viral entry obviously exist with every injection of blood, plasma or serum, and with injections of biologic products containing plasma or serum. The outstanding example of the latter is the U. S. Army outbreak in 1942 associated with the prophylactic injections of yellow fever vaccine. As you know, the yellow fever vaccine contained a small amount of serum which apparently was responsible for hepatitis virus transmission to tens of thousands of army personnel. Over 50,000 cases are thought to have been infected from this source.

More recently attention has been directed toward the possible transfer of these viruses by means other than intentional injection, namely, by the use of improperly sterilized syringes and needles. This is made possible by the resistance of the viruses to commonly used disinfectants and by the small quantity of serum (.01 cc. or less) required for transmission of the virus. The evidence of hepatitis virus transfer by this method is again indirect but nevertheless it is good enough to oblige us to face the reality until proved otherwise.

How does this occur? First of all, it is obvious that in attempting to withdraw blood from a vein with a syringe we may create considerable suction by pulling strongly on the plunger in an effort to obtain blood more rapidly. This often collapses the vein and the negative pressure very readily sets up conditions where there could be reflux back and forth between the vein and the syringe. Further, there is

evidence from England to show that when the tourniquet is released a momentary negative pressure in the vein is produced which is sufficient to withdraw a small quantity of blood from the needle.

In the procedure of using syringes and needles simply for injections it is common practice in immunization or therapeutic procedures applied on a mass basis to use the "single syringe-multiple dose technic" and simply to change the needle or perhaps just wipe the needle between patients. As many of us have been taught always to aspirate before injecting, it is quite possible in using this "single syringe-multiple dose technic" to contaminate the syringe contents with hepatitis virus from one person and then infect a group of persons with the multiple doses from the remainder of the contents.

Attention has been drawn to the possibility of transfer of hepatitis virus even by the finger puncture technic commonly used in doing blood counts. Ordinarily, the stylet or needle used for puncturing the finger is just washed off or immersed in alcohol and then is used on the next person.

Finally, it has been suggested that transfer may sometimes occur from syringes or needles used for injecting procaine, by dentists for example. There are so many potential sources that the problem becomes extremely difficult.

In Germany this summer, Dr. Havens and I had the opportunity to see approximately 300 cases of hepatitis in the U. S. Army Hepatitis Center. Of interest was the fact that nearly all of these patients had been exposed to some sort of parenteral procedure during the preceding six months.

I would like to conclude my discussion with a few words about infectious hepatitis and its modes of transmission. To date we know only that during the active disease the virus (IH type) may be present in the blood and feces. The problems relating to control in blood are the same as those discussed in relation to the serum hepatitis syndrome. The problems of transmission from feces involve all the possible direct

and indirect ways of transmission by contaminated water, food, milk, fomites, direct contact, mechanical transfer by flies, etc. This obviously puts the transmission of this disease and the problems of its control into the same category as some of the other enteric bacterial infections, with the added problem that the hepatitis viruses apparently are more resistant to procedures which ordinarily control bacterial agents.

There are a number of other aspects of hepatitis that are worthy of discussion but I have taken about all of my time and perhaps these other aspects will arise during the open discussion.

STUDENT: Has the recent extensive pathologic study of this disease brought out anything that would help to tell one type of hepatitis virus infection from the other by their histologic characteristics?

DR. NEEFE: I think that pathologists like Lucké and Mallory, who have done much of the recent work in this field, are agreed that they cannot distinguish what presumably is a case of virus SH hepatitis from virus IH hepatitis.

I might point out one interesting observation for what it is worth. How consistent or significant it is I do not know. Dr. Reinhold and I have been interested in the results of the various hepatic tests in these two types of hepatitis (IH and SH) and there does seem to be a difference in the response of the thymol and colloidal gold tests in the virus SH group as compared with the virus IH group. In a number of those who had virus SH hepatitis the thymol test either failed to become abnormal or became only weakly positive, whereas in the experimental virus IH hepatitis group the thymol and colloidal gold responses consistently were markedly abnormal. These trends were quite consistent in the experimental groups and while I do not think one can depend on them to differentiate the two diseases, because of individual exceptions, the observations have some clinical significance in the fact that a positive thymol test is not essential for the diagnosis of viral hepatitis. Some of the published results

had led us to expect that the thymol turbidity test would be positive during acute hepatitis but our own observations indicate that one should not necessarily expect a positive thymol test, particularly in virus SH hepatitis. The cephalin flocculation test was consistently positive in both groups, except for one case of virus SH hepatitis in which none of the "flocculation" tests became positive during the entire course of the disease.

DOCTOR: Is the sum total of your studies, Dr. Neeffe, plus those of Dr. Havens and others, adequate to say whether or not there is any consistent difference in duration of course in the prognosis of the two diseases?

DR. NEEFFE: I think the actual duration of the course cannot be considered significantly different in the experimental groups. When one considers the various series reported in the literature, it is a different story and it does seem that the pre-hepatitis condition of the persons involved is an important factor. This is a clinical problem which we face in civilian life in respect to serum hepatitis. Often occurring in older people, in persons who have been in a hospital for some other illness or who have had serious operations, the nutritional status frequently is poor before the onset of hepatitis and, moreover, other diseases may coexist. In battle casualties the same situation occurred. One group reported by Dr. Snell and others had an estimated mortality rate of 19 per cent. Yet, in the 1942 yellow fever vaccine outbreak, which involved army personnel who were healthy, well nourished and in good physical condition, the mortality and the morbidity, as far as we can tell, did not differ much from that observed in the epidemic or virus IH type under similar conditions.

DR. HANGER: Dr. Neeffe, I would like to ask a question which I am sure is in the mind of many in the audience. I would like to know how you at the University of Pennsylvania Hospital segregate your cases of acute hepatitis, what precautions you institute and when you relinquish these precautions.

DR. NEEFFE: I might say at the start that it is hardly possible to take all the precautions that seem indicated on the basis of our present knowledge. Our principal objective is to do all that can be done in a hospital to prevent transmission from feces and from blood. Patients are put on what might be called "intestinal isolation" in the same fashion as are typhoid patients. This is maintained until discharge from the hospital. As no one knows how long the virus persists in feces, the length of time such precautions should be maintained is purely a guess. We usually suggest that special care be taken until at least two weeks after jaundice disappears. Fortunately, the duration of hospitalization in the average case is not so long that continuation of "intestinal isolation" for the entire period becomes impractical.

Efforts to prevent transmission from blood should be directed toward diminishing the opportunities by which this may occur. This requires, among other obvious precautions, special attention to venous and finger puncture technics and to the whole question of the handling of syringes and needles. This matter was recently laid before the Subcommittee on Liver Diseases of the National Research Council by means of a formal direct request from one of the federal agencies for advice as to what procedures should be instituted regarding the routine handling of syringes and needles. The opinion of the Subcommittee was unanimous that all syringes and needles be properly cleaned and sterilized by heat before use in each patient. This presents a real technical problem for large hospital services and I do not know how it can be done in a simple way. It probably is the only certain way of eliminating the risk entirely. How great the risk is if one does not take these precautions is hard to define. However, as the evidence does indicate that failure to observe such precautions involves some risk, it is our obligation to recognize and eliminate the sources of risk insofar as possible. One way of simplifying the syringe problem to some extent is to eliminate the

use of a syringe for drawing blood specimens whenever possible. The use of a needle and a short piece of rubber tubing often suffices for collection of blood specimens, particularly small ones. The use of the "multiple dose—single syringe technic" for mass therapeutic or immunization procedures, although convenient, is to be condemned.

Although urine has not been proved to be a definite source of hepatitis virus, it seems wise to take the same precautions in handling specimens from hepatitis patients as are used in the management of typhoid cases.

There appears to be no conclusive evidence of nasopharyngeal droplet transmission of hepatitis virus during the active stages of the disease although such transmission, particularly during the incubation period, has not been excluded. At the present time, therefore, there seems to be no definite indication of any need for special measures, other than reasonable care, directed toward the prevention of droplet transmission from hospitalized patients during the *active* disease.

DR. HANGER: It is obvious that no uniform or satisfactory procedure is being followed in our general hospitals. I have recently written to the directors of a number of our leading medical clinics asking what routine has been inaugurated in their institutions to prevent the spread of hepatitis by contact and by venipuncture. The precautions enforced at all these places seem to be tempered with optimism and wishful thinking. In none, however, has a major outbreak of hepatitis been observed among patients or hospital personnel. It would, therefore, seem that a reasonable ward routine and the use of clean, dry syringes are quite effective in curbing the spread of this disease.

DR. ALBERT W. GROKOST: How soon after your patient with hepatitis is discharged do you use his bed?

DR. NEEFE: I think that the famous remark of Dr. Rivers is apropos, namely, that all of humanity is covered with a thin layer of human feces. Thus it appears that

the complete elimination of all sources of contact with virus in a hospital would require superhuman measures beyond the realm of possibility at the present time. Disinfection of the bed linen and blankets, of course, is easily accomplished. Bedside and other utensils can be disinfected with relative ease. The bed mattress is more difficult and whether it is sufficiently important to require some special means of disinfection is unknown. In other words, it does not seem practical at the present time to delay for long the re-use of hospital beds.

DR. HANGER: We might turn now to a consideration of the more chronic forms of hepatitis and their management. I know of no series of cases that have been better studied than those involving Navy personnel observed at the Rockefeller Hospital during the war. Dr. Kunkel, with his associates Dr. Labby and Dr. Hoagland, were able to follow the course of the disease with a wide variety of tests by which the therapeutic value of diet and various medications could be appraised. They have also noted the criteria by which the transition from acute hepatitis to the chronic form can be recognized. Dr. Kunkel will talk to us on these two important aspects of hepatitis.

DR. HENRY G. KUNKEL: For a proper discussion of the treatment of infectious hepatitis and its sequelae it is necessary to consider in some detail the types of chronic liver disease that may develop after an attack of infectious hepatitis. This problem is of particular importance at the present time because the chronic complications of the many cases which occurred during World War II are now beginning to become evident.

The experience derived from a follow-up study of 400 Navy men with acute infectious hepatitis who were admitted to the Rockefeller Hospital during 1944 and 1945 permits certain conclusions to be drawn regarding the chronic aspects of the disease. The most common complication observed in this group was a relapse during convalescence which occurred in 15 per cent of the patients. This was readily detected by a rise in

bromsulfalein retention and in values for the thymol turbidity test. During normal convalescence the bromsulfalein retention falls to normal along with the bilirubin level. The thymol turbidity of the serum falls somewhat more slowly. In the patients suffering relapse the bromsulfalein retention suddenly rose again and remained elevated for from two weeks to three months. The thymol turbidity of the serum also rose but much more slowly and remained abnormal for as long as six months. The bilirubin level of the serum remained normal throughout the period of relapse except in the very severe cases. Associated with these changes in liver function was a return of mild symptoms of liver tenderness, anorexia and fatigue. In almost every case the relapse followed the period when the men were first returned to full activity. It appeared as if the liver were unusually sensitive to further damage through exercise during this period.

As soon as a relapse was detected, the men were returned to bed until values for bromsulfalein retention returned to normal. All but two of the patients suffering relapses recovered uneventfully. These two showed slight persistent signs of liver insufficiency along with intermittent bromsulfalein retention for more than eighteen months after the period of relapse.

A second group of four patients never showed significant improvement following the initial attack of infectious hepatitis and developed a severe chronic hepatitis. At the present time, two years after the initial attack, they still show marked fatigue on exertion, episodes of liver tenderness and marked bromsulfalein retention. These patients appear to have early cirrhosis of the liver.

A third group of seven patients showed a persistent selective abnormality in bilirubin metabolism although all other liver function studies were normal. The bilirubin level of the plasma remained slightly elevated for more than one year after the initial attack. Three of the seven patients continued to have symptoms of fatigue along with bilirubin elevation.

The patients that have been discussed thus far were those who showed a divergence from normal convalescence. The remainder of the 400 patients were discharged free of symptoms and with normal liver function tests after the initial attack of infectious hepatitis. However, follow-up studies have indicated that approximately 60 per cent of this group have shown symptoms attributable to liver dysfunction at some time during the past two years. The symptoms in order of frequency are as follows: undue fatigue, drowsiness, intolerance to alcohol, liver tenderness and intolerance to fatty foods. Liver function tests carried out in these individuals have shown very little impairment. They are all gradually recovering completely and the possibility of serious complications in this large group appears remote.

None of the group of 400 patients who have been followed from the onset of the initial attack of infectious hepatitis has developed ascites or other evidence of severe cirrhosis. However, the fact that a severe and sometimes fatal cirrhosis may develop following infectious hepatitis is clear from studies carried out in four other young service men who incurred their initial attack under wartime conditions. Laparotomy biopsy or autopsy material was available in each case. The gross appearance of the liver was unusual in all of the four patients, being characterized by an irregular nodularity. Large nodules 1 to 2 inches in diameter were prominent. Sections of the liver showed that these nodules were large masses of regenerated liver cells without a lobular pattern. Surrounding these nodules were dense areas of fibrous tissue without any liver cells. The picture was different from the usual Laennec's cirrhosis and most closely resembled the post-necrotic type of cirrhosis originally described by Mallory.

With this brief introduction to the chronic complications that may ensue following infectious hepatitis, we might go on to consider the therapy of this disease during the acute and chronic stages. Two main types of therapy have been proved to be of value during the acute stage: (1) bed rest; (2)

dietary regulation. The value of prolonged bed rest was clearly established by numerous army groups who investigated the disease, as well as by our own study. The time necessary for liver function tests to fall to normal following the institution of bed rest therapy

group. These studies indicate that strict limitation of fat in the diet actually has some harmful effects. The anorexic patient with acute infectious hepatitis finds a low fat diet very unpalatable and continues to lose weight. Therapy should be directed mainly

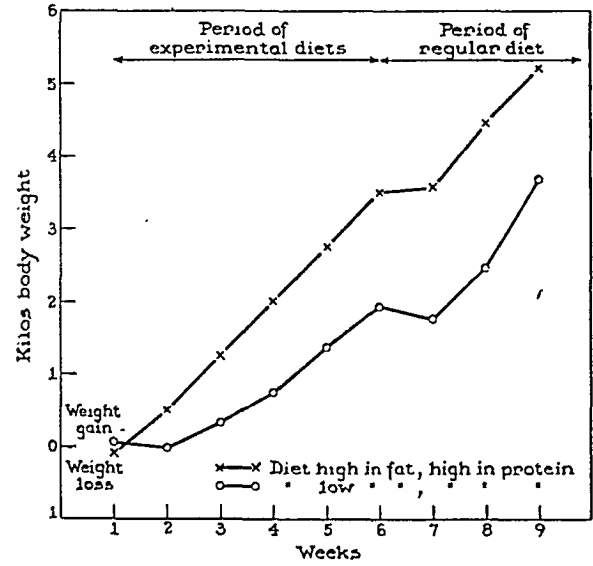


FIG. 2. A comparison between the average weekly increase in weight in a group of thirty-seven patients with infectious hepatitis on a diet high in protein and high in fat and that in thirty-three patients on a diet high in protein and low in fat.

was approximately the same regardless of how long after the onset of the illness the patients were started on this therapy. The development of relapses following the first period of activity attested further to the value of bed rest during the acute stage of the disease. Our patients were kept in bed as long as any impairment in bromsulphalein excretion was present.

The second point, dietary therapy, has been the subject of much dispute. When we began our program the dictum against the inclusion of fat in the diet of patients with acute liver disease was firmly established. However, controlled studies on the effect of a high fat diet versus a low fat diet in patients with infectious hepatitis demonstrated that the high fat group improved more rapidly than the low fat group. Figure 2 illustrates the more rapid weight gain in the high fat group. The time necessary for the bromsulphalein retention to return to normal was slightly shorter in the high fat

TABLE I
COMPARATIVE EFFECTS OF METHIONINE, CHOLINE, LIVER EXTRACT AND SALINE ON THE AVERAGE PERIOD REQUIRED FOR RECOVERY IN PATIENTS WITH INFECTIOUS HEPATITIS

Medication	No. of Patients	Net Change in Weight in Hospital (Kg.)	Average Duration of Illness (Days)
Intravenous methionine..	16	+2.9	53.5
Oral choline.....	29	+3.1	50.7
Intravenous crude liver extract.....	34	+3.5	48.9
Intravenous saline (control group).....	31	+3.1	51.5

toward increasing the caloric intake as much as possible during the acute stage of the disease in order to return the patient to positive nitrogen balance and permit him to regain the initial loss in weight.

With respect to the other substances which have been advocated for the treatment of acute hepatitis, methionine, choline, liver extract, amigen, etc., no definite evidence is available that they are of value for this purpose. Table I illustrates the comparative duration of illness in three groups of patients with various supplements to a standard diet. The control group did just as well as the other groups given methionine, choline and liver extract.

In the severely ill or comatose patient with acute infectious hepatitis protein should be administered in the form of concentrated plasma albumin or whole plasma. Continuous infusions of glucose are necessary to provide an adequate caloric intake. Intravenous administration of amino acids proved of little value because of their rapid excretion.

When the patient has recovered from the acute stage of infectious hepatitis and his plasma bilirubin and bromsulfalein retention have fallen to normal, he should be observed very closely for the possible development of a relapse following a return to

poor appetite the administration of intravenous liver extract has brought about improvement.

A characteristic feature of the later stages of this disease is the extreme liver damage that is present, manifesting itself in very low

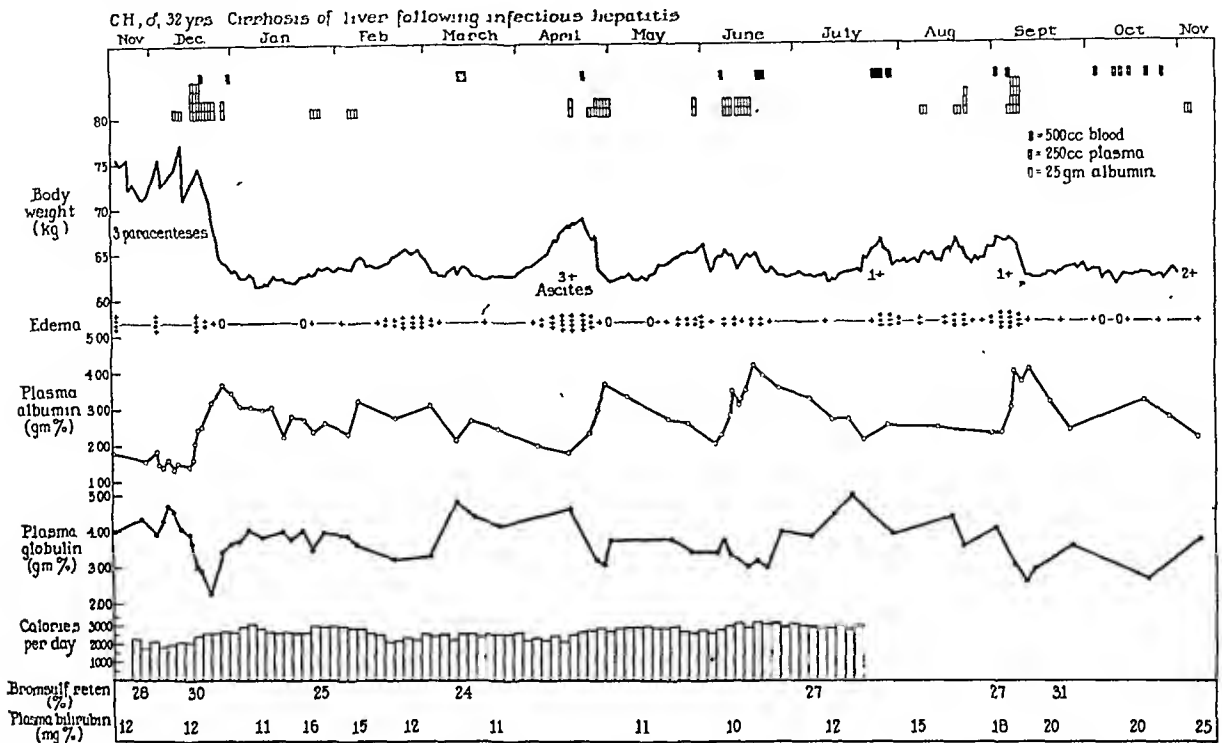


FIG. 3. Course of a patient with cirrhosis and generalized anasarca eighteen months after infectious hepatitis showing rapid and complete loss of edema and ascites following 27 units of albumin and control of recurrent ascites with additional albumin. Death was due to uncontrollable bleeding tendency.

activity. This is a critical period and liver function tests should be carried out with special care. With the appearance of the slightest sign of relapse the patient should be returned to bed. The importance of such therapy has been emphasized by the severe course of the illness in certain patients who suffered relapses under wartime conditions and were forced to continue activity. The early detection and treatment of relapses is perhaps the most important aspect of the care of patients with infectious hepatitis.

The treatment of chronic hepatitis and post-hepatitis cirrhosis is a difficult problem. Once cirrhosis has become established, the disease takes a malignant course and is but little amenable to the usual dietary forms of treatment which are valuable in Laennec's cirrhosis. In an occasional patient with

plasma albumin levels. The administration of concentrated human albumin is of dramatic temporary benefit in these patients. Figure 3 illustrates the course of a Navy veteran who developed severe cirrhosis following a relapse of infectious hepatitis under wartime conditions. Ascites and edema appeared and did not respond to dietary therapy. Following the administration of approximately twenty-seven 25-Gm. units of human albumin, diuresis occurred with loss of all ascites and edema. The general condition of the patient improved greatly and he led a normal life for approximately three months. Hepatic function did not improve, however, and the plasma albumin level gradually fell, resulting in further edema and ascites. This could be readily controlled by the administration of more albumin and the

patient was kept virtually free of ascites for approximately one year. He finally died as a result of a marked bleeding tendency from his mucous membranes, a manifestation of severe liver damage attributable to deficient production of prothrombin and fibrinogen. However, it was believed that albumin therapy probably prolonged his life for almost a year.

DR. SIDNEY C. WERNER: Dr. Kunkel, was there a corresponding fall in globulin in the serum when you gave albumin?

DR. KUNKEL: The globulin in the serum fell initially with the albumin administration. This is purely a hemodilution effect, a result of the increase in plasma volume. Electrophoretic patterns have furnished further evidence that the fall in globulin is due solely to hemodilution.

DR. DANA W. ATCHLEY: I would like to ask how much emphasis you place on foregoing carbohydrate.

DR. KUNKEL: Carbohydrate was furnished in the diet in an amount necessary to meet the calorie requirements of the individual. Additional carbohydrate was not given because this would tend to lower the protein and fat consumption.

DR. ATCHLEY: Why do you prefer to give liver intravenously? Do you not think that the same amount intramuscularly would affect the appetite to the same degree and produce an equal therapeutic effect?

DR. KUNKEL: By intravenous administration it is possible to give larger amounts of liver extract with less discomfort to the patient. These larger doses appear to increase the appetite considerably more than small intramuscular administrations.

DR. HANGER: The crude liver that you were giving was the commercial product Intraheptol?

DR. KUNKEL: Yes.

DOCTOR: What are your present views concerning intravenous liver therapy in liver disease?

DR. KUNKEL: In patients with complications following infectious hepatitis, we never found it to be of dramatic benefit; in some instances improvement in appetite and gain

in weight occurred, but in no instance was there any significant change in the results of liver function tests. However, in patients with the nutritional type of cirrhosis, i.e., classic Laennec's cirrhosis, we believe liver extract is of definite value. This we believe is also due to improvement in appetite and in the general nutritional state.

DR. ATCHLEY: Nobody mentioned the important problem of alcohol. Abstinence is important during the acute stage but how long before a man becomes a citizen again?

DR. KUNKEL: We usually advise against alcohol for at least three months after an attack of infectious hepatitis. After that we leave it up to the patient himself. Intolerance to alcohol was one of the commonest complaints in patients with mild symptoms of a lingering hepatitis and as a result they stayed away from it. It appeared as if alcohol has a specific bad effect on the liver in these border line states. The patients who recovered completely tolerated alcohol without difficulty within a few weeks after an attack of hepatitis.

DR. ATCHLEY: Have you seen any specific relapse based upon overindulgence in alcohol during the convalescent period?

DR. KUNKEL: Yes, the one severe relapse of our group, with return of clinical jaundice, occurred in a patient who did considerable drinking as soon as he left the hospital.

DR. ATCHLEY: You emphasized activity entirely when you were discussing relapses. I wonder whether the amount of activity would be a factor there?

DR. KUNKEL: It was the impression that overactivity was more prone to cause relapses in the convalescent period. However, there was no doubt that even mild activity sometimes brought on a relapse.

DR. ATCHLEY: Was alcohol a factor in the people who developed a fatal cirrhosis?

DR. KUNKEL: It may have been in one case but not in the others.

DR. KENNETH B. TURNER: What is the mechanism of the relapse?

DR. KUNKEL: That is a very difficult question. Whether it results from a persistent

virus which is re-activated or whether it is purely a metabolic disturbance is not known. Dr. Neefe's experiments, we hope, will answer this important question.

STUDENT: I wonder if Dr. Neefe would like to say a word or two about the persistence of the virus in the group of patients that Dr. Kunkel has been talking about. In the type of hepatitis in which you induce the disease, Dr. Neefe, are factors other than the initiating cause responsible for persistence of the disease, or is there a persistence of the virus itself?

DR. NEEFE: Of our volunteers with induced hepatitis, several had a persistence of symptoms resulting in partial disability for a prolonged period after subsidence of acute manifestations of hepatitis, what one might call a chronic, non-icteric, active hepatitis. We collected a number of feces and serum specimens from these subjects through the period of approximately one year during which the symptoms and abnormal findings in respect to the hepatic tests continued. In addition, one subject had a liver biopsy obtained by laparotomy and a small portion of the liver specimen was frozen to be available for testing. These three materials were administered to separate groups of volunteers with the hope of determining whether or not virus was present in these materials during this period after the subsidence of the acute disease. If present, one might postulate that the virus had something to do with the persistence of the symptoms and abnormal findings. Unfortunately, the results of the experiment were not conclusive. There were five men who were given the liver biopsy material and, about twenty-eight days after inoculation, one of the men developed an acute illness characterized by marked abdominal pain, anorexia, nausea, vomiting and definite enlargement and tenderness of the liver. However, he failed to develop some of the changes that we usually find with acute hepatitis, namely, evidences of marked disturbance in liver function, and, of course, he did not develop jaundice. He did have a minor degree of bromsulfalein retention, but not more than

one might see during the course of almost any acute illness. Because of the time of the onset of symptoms after inoculation and the definite enlargement and tenderness of the liver, one would certainly be inclined to call the disease hepatitis were it not for the absence of definite laboratory evidence of hepatic disturbance. Similar but less acute manifestations occurred in several of the men who received the feces but again the laboratory findings were not conclusive. Thus, we were left with a situation in which something had happened but could not be interpreted. The volunteers who received the serum were, in a sense, a fairly good control group in that they showed no abnormalities in the way of symptoms or signs. One can only say, therefore, that there was a suggestion that something was present in the materials administered that caused some sort of illness. Exactly what it was we could not determine. It is hoped that it will be possible to attempt to transfer the disease further to other volunteers by using serum and feces obtained from these men. Unfortunately, this has not been possible to date. As far as I know this is the only direct attempt to demonstrate persistence of virus in chronic cases and unfortunately it leaves us still in the dark.

SUMMARY

DR. HEATH: Infectious hepatitis has been shown in recent years to be a viral disease. For despite the fact that the virus has never been isolated or visualized, despite the fact that characteristic lesions have never been produced in the chick embryo or the virus grown in tissue culture, despite the failure to demonstrate inclusion bodies in infected material and despite the failure to find a susceptible laboratory animal, the work of Neefe and others using human volunteers has conclusively shown that an agent can be isolated from human cases of infectious hepatitis which will reproduce the disease when administered to other human beings.

This infectious agent passes bacteria-retaining filters, is not destroyed by ordinary bacterial disinfectants, survives 56°C. for one

hour and remains infectious under a wide range of conditions. On the other hand, it may be inactivated in plasma on exposure to ultraviolet light and under certain conditions may be destroyed when subjected to 60°C. for several hours.

So far, at least two distinct varieties of hepatitis-producing agents have been identified, the IH and SH strains. The former, isolated from cases of epidemic infectious hepatitis, would appear to be the more widespread and common agent. After inoculation it produces symptoms, often with fever, in twelve to forty-two days although the incidence of takes is considerably higher (80 per cent) when the material is given orally than when injected parenterally. The resulting disease cannot be distinguished either pathologically or in its clinical course from that due to SH virus, except that gamma globulin when given during the incubation period protects against or modifies the IH disease, but so far has not been shown to be active against the SH disease.

SH virus can be inoculated successfully (75 per cent) only by the parenteral route and then exhibits a prolonged incubation period of 60 to 300 days, during which time the virus is present in the blood. The thymol turbidity test may be negative in SH hepatitis.

During the period of active jaundice viremia is common to both diseases and presumably the virus may be found in the stool in each case (though demonstrated only in IH), but how long either of these phenomena persists after recovery is not known. Each virus infection is followed by the development of long-term specific immunity, presumably permanent, but there is no cross-immunity.

How infectious hepatitis is transmitted is not entirely clear. A certain number of cases due to IH virus apparently follow the ingestion of infected material. But accidental transmission of both IH and SH virus may follow upon improper handling of needles and syringes so that adequate heat sterilization of these implements and avoidance of the "multiple dose—single syringe" technique seems essential. Sterilization of feces,

urine, bedside utensils, bed linen and blankets is also recommended. When these measures have been carried out, accidental transmission of either virus has not been a problem.

The hepatic lesion in virus hepatitis may have three components:

1. *Parenchymal damage* is associated with a positive cephalin flocculation test, elevation of the direct serum bilirubin and impaired liver function as measured by galactose tolerance and cholesterol esterification.

2. *Involvement of the reticuloendothelial system*, i.e., the Kupffer cells and the sinusoidal lining, leads to hyperglobulinemia and portal obstruction as evidenced by splenomegaly, ascites and elevation of indirect serum bilirubin and serum alkaline phosphatase.

3. *Periportal inflammation* may produce abnormalities of both types noted above.

Some 60 per cent of patients following recovery from acute hepatitis may have symptoms such as fatigue, drowsiness, fatty food and alcohol intolerance, in addition to physical findings such as liver tenderness, without any detectable abnormality in liver function tests. In the 15 per cent with definite relapse the laboratory findings are usually limited to bromsulfalein retention and positive flocculation tests, although in instances of severe relapse, jaundice may recur with alteration in other tests as well.

Therapy of the acute disease is limited chiefly to bed rest and dietary measures. The former should be complete and prolonged until the bromsulfalein retention is normal since too early activity may be responsible for relapse. A high calorie diet with high protein and, after the first few days of anorexia and fatty food intolerance, high fat content seems most desirable at the present time. Liver extract intravenously may stimulate the appetite, especially in chronic cases, but it should be emphasized that ordinary liver extract prepared for intramuscular injection cannot be so used. Finally, in patients with edema and ascites on the basis of hypoalbuminemia, the administration of plasma or human albumin may be temporarily beneficial.

Clinico-pathologic Conference

Recurrent Progressively Severe Headaches Leading to Coma and Death*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. E., (B. H. No. 141717), a forty-six year old tavern keeper, entered the Barnes Hospital on December 4, 1946, complaining of headaches. The family history was of interest only in that the patient's father had died at the age of sixty-four of Bright's disease. The past history was significant in that at the age of twenty the patient developed a chancre on the lip. A diagnosis of syphilis was made by a physician after three serologic tests had been positive. The patient was treated with six injections of "606" and by oral medication given in drop doses. Subsequently, three other serologic tests were negative. At the age of twenty-two the patient had an episode of abdominal pain and was told by a physician that he had a peptic ulcer; the diagnosis was said to have been confirmed by roentgen ray examination. The gastrointestinal symptoms recurred periodically thereafter but had been absent for three or four years prior to the patient's admission to the hospital. Otherwise, he had enjoyed good health. He was a cafe owner and had cooked and attended bar; he stated that he drank approximately 1 pint of hard liquor daily.

The patient was apparently well until three weeks before admission when a particle of food lodged in his throat. As a result, he experienced paroxysms of coughing and during one of these he developed a sudden pain behind the right eye which was de-

scribed as quite severe. The pain recurred daily thereafter lasting five minutes to five hours. It was aggravated by cough and not relieved by any medication. The episodes of pain were characteristically sudden in onset and disappeared just as rapidly; they occurred chiefly during the day and rarely at night. No dizziness, faintness or other symptoms were noted until five days before entry when the headaches became associated with vomiting. Over a period of five days the patient vomited approximately twelve times. There was no accompanying nausea but a poorly defined unpleasant sensation was said to have preceded the episodes of emesis. In the three weeks during which he had symptoms the patient lost approximately 20 pounds.

At the time he entered the hospital physical examination revealed his temperature to be 36.6°C., pulse 54, respirations 16 and blood pressure 120/70. The patient was a well developed, well nourished male who lay flat in bed; he held his hand over his eyes and complained of generalized headache. He seemed depressed and gave only the briefest answers to questions. The pupils reacted sluggishly to light and accommodation but were round, regular and equal. Examination of the optic fundi showed the discs to be clearly outlined but the veins appeared full. The teeth were dirty and the breath was foul. Examination of the lungs was entirely negative. The heart was not enlarged and

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

the rhythm was regular; the sounds were normal in quality and there were no murmurs. The abdomen was soft; the liver edge could be felt just at the costal margin but no other organs or masses were made out. Rectal examination revealed only minimal prostatic enlargement. Neurologic examination was essentially negative.

Laboratory data were as follows: Blood count: red cells, 5,060,000; hemoglobin, 15.2 Gm.; white cells, 8,600; differential count: eosinophiles, 1 per cent; stab forms, 15 per cent; segmented forms, 62 per cent; lymphocytes, 20 per cent and monocytes 2 per cent. Urinalysis: albumin, trace; sediment, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 17 mg. per cent; blood sugar: 71 mg. per cent. Roentgenograms of the skull: indeterminate.

During his hospital stay the patient had very frequent headaches and he remained dull and depressed. Codeine and aspirin gave him little or no relief. Early in the evening of his third hospital day the patient seemed confused and his conversation was without continuity. Later that night he was found on the floor adjacent to the bed. It was not known whether he had fallen out of bed or had slipped after getting up. He was examined carefully and no evidence of injury or additional abnormal physical findings were found. Four hours later the call light outside his room went on and when the nurse arrived a few seconds later she again found the patient on the floor, this time with a small laceration over the occiput. He was again examined by a house officer and responded readily to questions but his answers were definitely confused. He rapidly became stuporous. On examination the blood pressure was 130/80 and the pulse rate 60. The eyes were turned to the left and the pupils, although small, were equal and reacted to light and accommodation. The fundi appeared as they had at the time of the original examination. The neck was not stiff. The extremities were spastic, the lower ones especially so, and bilateral pathologic toe signs and ankle clonus were elicited. The abdominal reflexes were absent.

The patient became extremely hyperactive and difficult to restrain; he was therefore given 12 cc. of paraldehyde by mouth and following administration of the drug he quieted down so that he could be controlled. During the course of the next few hours spasticity increased, particularly on the right side, and the neck was said to have become somewhat stiff. However, it could not be determined whether the stiffness was attributable to the state of generalized rigidity or due to true meningeal irritation.

Two hours later the patient's pulse rate had risen to 120. Respirations were regular, deep and stertorous. Spasticity of the extremities appeared to have decreased to some extent. The patient was seen in consultation by a neurologic surgeon and a lumbar puncture was advised. This procedure was performed with great care; the initial pressure was 350 mm. of water and the fluid appeared clear. After 2 cc. had been removed very slowly the patient stopped breathing and in spite of artificial respiration and other emergency measures he could not be revived. Subsequently, a Wassermann test on the spinal fluid was reported as negative. Death occurred on December 7, 1946.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: This case presents one of the most difficult diagnostic problems that we have faced for some time in these conferences. The patient suffered primarily from a neurologic disorder and we shall rely on Dr. Jones, who saw the patient in consultation, and on Dr. Levy for aid in our attempt to reach a diagnosis. It seems advisable to divide the discussion into two parts: First, we shall try to localize the lesion in the central nervous system and secondly, we shall discuss the possible causes of the lesion. Dr. Jones, I believe you saw this patient after he had fallen out of bed on his third day in the hospital. According to the history, he was given paraldehyde shortly before the accident. From your examination at that time what was your impression as to the site of the principal lesion?

DR. ANDREW B. JONES: At that time I thought that the mid-brain and the upper pons were involved.

DR. WOOD: Could you tell us specifically the signs that you considered important?

DR. JONES: The rigidity and spasticity of the lower extremities, the bilateral pyramidal tract signs and the pathologic toe signs all seemed significant.

DR. WOOD: Could a lesion in any other part of the brain give rise to those signs, Dr. Jones?

DR. JONES: Not that I know of. I should like to qualify my statement, however, by stating that the lesion itself would not have had to be in that location but would have to be in a position to exert pressure on that portion of the brain.

DR. WOOD: May such signs be seen in subarachnoid hemorrhage if, as a result of the bleeding, there is irritation of the brain?

DR. JONES: I cannot recall that I have ever seen such a clinical picture.

DR. WOOD: What causes would you think of here, Dr. Levy, other than a lesion in the mid-brain or pons? Can we dismiss involvement of any other part of the nervous system?

DR. IRWIN LEVY: It seems to me that hemorrhage into the ventricle is a possibility. I did not see this patient but considering the signs already discussed and adding the facts that the patient was described as looking to the left, that his right side showed more involvement than the left and that he was unconscious, one would be justified in entertaining a diagnosis of interventricular hemorrhage.

DR. WOOD: Dr. Jones, would you mind describing for us again the signs as you found them?

DR. JONES: At the time that I saw the patient he was in coma and could not be roused by any stimulus. His head and eyes were turned to the left. There were very rapid movements of both eyes but occasionally one eye would deviate. The neck was not stiff but the extremities were spastic and were held rigidly in extension. There

were pathologic toe signs. Occasionally, the upper extremities would relax.

DR. WOOD: Did you consider the possibility of hemorrhage into a ventricle as suggested by Dr. Levy?

DR. JONES: Yes, I thought of it but because the head and eyes were turned to one side, I thought more of a vascular lesion in the mid-brain or pons or of some lesion other than hemorrhage exerting pressure on this area. Ventricular hemorrhages may cause spasticity but as a rule the pupils are small and the signs are more equal bilaterally. The signs in this case, although they were somewhat symmetrical, were more pronounced on the right.

DR. WOOD: Dr. Levy, it is interesting that when Dr. Henry Schwartz saw this patient he made the same diagnostic suggestion that you have made, namely, hemorrhage into the ventricle. We seem then to have two possibilities—a lesion in or about the pons or a large hemorrhage into the ventricle. Have you any comments to add concerning the localization of the lesion, Dr. Charles?

DR. BEN H. CHARLES: No, there is little that I can add. When I first saw the patient, there were no localizing signs.

DR. JONES: Dr. Wood, this patient was admitted to the hospital because of headaches. In other words, he had headache before he fell and sustained his injury. When I saw him immediately after his injury, I considered the possibility of epidural or subdural hemorrhage. In the light of the history, however, the possibility of a brain tumor should also be kept in mind.

DR. WOOD: If the patient had a brain tumor, would it have had to lie in the region of the medulla or the pons?

DR. JONES: Yes, or else it would have had to be in an adjacent area so as to exert pressure in that region.

DR. WOOD: Dr. Levy, can the possibility of interventricular hemorrhage be eliminated in view of the clear spinal fluid?

DR. LEVY: While the finding of clear spinal fluid certainly constitutes evidence against ventricular hemorrhage, occasion-

ally there is a delay in the appearance of blood in the lumbar fluid. The lumbar puncture was done shortly after the accident and it is conceivable that this case represents one of those instances in which the blood had not yet reached the lumbar space.

DR. WOOD: How would you explain the headaches and vomiting which the patient had prior to entering the hospital, some three weeks before his fall?

DR. LEVY: It is recorded that the patient coughed and had sudden pain behind the right eye. If the hemorrhage had been interventricular, it would have been due to a ruptured vessel on the left, probably in the left hemisphere. The pain behind the right eye on coughing suggests a stretching effect on the large vessels at the base of the brain. The possibility of central nervous system syphilis must also be considered. I do not know the significance of the fact that his pupils were described as sluggish.

DR. JONES: I do not agree with Dr. Levy for it seems to me that the possibility of interventricular hemorrhage need not be considered further in view of the fact that blood was not found in the spinal fluid.

DR. WOOD: Dr. Turner, would you restate the sequence of events and specify the exact interval between the accident and the lumbar puncture.

DR. GLENN O. TURNER: The patient was found out of bed for the first time about 3 A.M. and the next time, some four hours later, about 7 A.M. The lumbar puncture was not done until approximately noon.

DR. LEVY: I still think that the five-hour interval between the occurrence of the second fall and the performance of the lumbar puncture does not rule out interventricular hemorrhage. I am interested in the initial pressure of 350 mm.; unless, as Dr. Jones suggests, there was a tumor, the finding of an initial spinal fluid pressure of 350 mm. is compatible with an acute accident and suggests hemorrhage.

DR. WOOD: Why should this man have had a cerebral hemorrhage? He was in his forties and apparently in good health.

DR. LEVY: In view of the fact that his blood pressure was normal, rupture of a congenital aneurysm seems the most likely cause. Syphilis must also be considered.

DR. WOOD: Dr. Scott, may we rule out syphilis on the basis of the negative spinal fluid Wassermann?

DR. VIRGIL C. SCOTT: Syphilis cannot be ruled out completely but it seems very unlikely.

DR. WOOD: Dr. Jones, would you care to make a definitive diagnosis at this time?

DR. JONES: I should like to repeat that when I first saw the patient I was asked to see him because of his fall; after I had examined him the entire history was presented to me and I learned that he had come into the hospital because of previous headaches and vomiting. Therefore, although my original impression was that he had had a vascular accident secondary to immediate trauma, the occurrence of symptoms prior to admission made such a diagnosis unsatisfactory and I believed that the patient may have had a tumor.

DR. WOOD: Will you localize the tumor for us?

DR. JONES: I do not believe that the tumor was in the pons but rather in the region adjacent to it. The signs seemed to represent so-called "neighborhood signs." The tumor was probably a large one and therefore the most likely site would be in the cerebellum. Also, there may well have been hemorrhage into the tumor.

DR. WOOD: The man's entire illness covered a period of only three weeks. What type of tumor can grow rapidly enough to give rise to the symptoms recorded and also be the site of a hemorrhage?

DR. JONES: The exact type of tumor would depend somewhat on the age of the individual.

DR. WOOD: Was this man too old for a medulloblastoma?

DR. JONES: I cannot answer your question with certainty although medulloblastomas are more common in children.

DR. LEVY: Dr. Wood, I still am unable to believe that this patient had a tumor. The

history seems to me much more in keeping with a vascular accident.

DR. JONES: I agree that the original episode which was described, that is, a paroxysm of coughing and pain behind his right eye is very suggestive of an aneurysm near the bifurcation of the internal carotid artery. I do not believe, however, that the subsequent course can be explained by that diagnosis.

DR. WOOD: We have had the benefit of the opinions of two expert neurologists and have been unable as yet to reach a definitive diagnosis. Dr. Turner, you took an active part in the care of this patient. Do you have anything to add?

DR. TURNER: I should like to reemphasize the fact, stated in the protocol, that the patient became extremely hyperactive, so much so that all available personnel could not restrain him. It was for that reason that he was given the paraldehyde and when he subsequently quieted down we were able to perform a satisfactory neurologic examination.

DR. WOOD: I should like to suggest one more possibility for discussion before Dr. Moore describes the pathologic findings. This man was an alcoholic and I believe we should therefore consider the possibility of the acute hemorrhagic encephalitis which occurs in alcoholics and which may lead to their death in a relatively short period of time. I am referring to Wernicke's syndrome. Several of the patients originally described by Wernicke died in a period of two to three weeks. The lesions are located primarily in the region incriminated by Dr. Jones, and the spinal fluid is often normal despite the fact that there may be bleeding into the brain itself. I should like to ask both Dr. Levy and Dr. Jones whether the diagnosis of Wernicke's syndrome can be ruled out with certainty.

DR. LEVY: I think the fact that the patient died suddenly after lumbar puncture is against that diagnosis and I also think the initial spinal fluid pressure was too high.

DR. JONES: I considered the possibility, particularly before the results of the lumbar

puncture were known. However, the usual cranial nerve findings were not present and I also discarded the diagnosis.

DR. WOOD: Are there any other comments or suggestions?

DR. PALMER H. FUTCHER: I favor the presence of a tumor in this patient although he did not have papilledema. There apparently was a mass in the cerebellar area causing an increase in intracranial pressure. I have seen patients with metastatic carcinoma of the brain in the past who have baffled the clinicians; and although no primary site seems obvious, the possibility must still be considered. The patient had coughing paroxysms and conceivably could have had a pulmonary lesion. He also had had gastrointestinal complaints although these were so longstanding that the possibility of carcinoma of the gastrointestinal tract seems less likely.

DR. WOOD: The suggestion is a good one and certainly cannot be ruled out.

MEDICAL STUDENT: Could the cough have been a precipitating factor of hemorrhage within a tumor?

DR. LEVY: Hemorrhage in a tumor is not particularly common. I do not believe that cough is often a precipitating factor.

DR. WOOD: In summary, the diagnostic possibilities in this case include a neoplasm of the central nervous system, either in the region of the medulla or pons or in an area close enough to exert pressure on the mid-brain. Dr. Levy has defended the possibility of interventricular hemorrhage on the basis of a congenital aneurysm. Wernicke's syndrome was considered and finally Dr. Fletcher suggested the possibility of metastatic carcinoma from the lung.

Clinical Diagnoses: ? Neoplasms of brain in or near pons, ? primary, ? metastatic from lung; ? interventricular hemorrhage from congenital aneurysm.

PATHOLOGIC DISCUSSION

DR. JAMES G. OWEN: When the cranial cavity was opened, there was no blood either in the extradural, subdural or subarachnoid spaces. The brain when removed was found

to be of normal weight, 1,400 Gm. Step sections in the cerebral hemisphere showed slight symmetrical dilatation of the lateral and third ventricles, which contained no hemorrhage. The ependyma was pale and not discolored. The right hemisphere of the cerebellum was flat and very soft, bluish-green in color, and the folia of the right hemisphere were quite obscure. At the time the brain was removed from the cranial cavity the outer surface of the right cerebellar hemisphere shelled off and revealed a large, soft, brownish-red clot. On section of this hemisphere a large cavity was seen on the right, filled with a soft, friable blood clot and lined by a shaggy, greyish, translucent mass. In the base of this mass there was a large friable, reddish blood clot. The hemorrhage and greyish tumor tissue extended inward to obscure the dentate nucleus. The portions of the medulla and the pons in this area were distinctly distorted and were pressed downward and to the left. The fourth ventricle was slightly dilated.

The other important findings at the time of autopsy were in the lungs which were expanded and heavy, weighing 1,750 Gm. On cut section a frothy, watery, serosanguineous fluid exuded. At the apex of the left lung there was a large, flat, irregular mass which was firm, white and very tightly adherent to both the parietal and visceral fluid. The tumor formed a dense cap over the apex of the left lung, extending immediately downward to become tightly adherent to the arch of the aorta just distal to the origin of the left subclavian artery. On section the tissue was firm, white, flecked with yellow and sharply demarcated from the underlying lung tissue. There were two small tumor nodules elsewhere in the upper part of the lower lobe of the left lung. Two hilar lymph nodes on the left showed similar masses. There were no signs of ulcerations in the gastrointestinal tract.

DR. ROBERT A. MOORE: On the basis of the gross examination, we were able to make several diagnoses: First, we made a diagnosis of a tumor involving the pleura of the

left lung, the tracheobronchial lymph nodes and the cerebellar hemisphere. There was hemorrhage into the tumor in the cerebellum of considerable size. On the basis of the gross examination the type of tumor cannot be stated with certainty although two possibilities stand out. First of all, the tumor in the lung and the tumor in the brain may have been unrelated; in other words, this patient may have had two separate tumors, the one in the cerebellum, a glioma, and the lesion in the lung being primary there. Secondly, the patient may have had a primary tumor of the lung which metastasized to the brain. If the latter postulate is correct, there are again two possibilities: one that the primary tumor arose in a bronchus at the apex of the lung, in other words, a so-called Pancoast tumor. Actually, it had not yet become a Pancoast tumor for it had not crossed the pleura and involved the structures that are typically involved in that syndrome. In other words, the tumor may have been a simple tumor of the pulmonary apex without further involvement. Also the possibility exists that the tumor was a mesothelioma primary in the pleura at the apex of the lung.

Turning to the microscopic sections for our answer Figure 1 shows a section of the pulmonary tumor and one sees that it is of an alveolar type. The next section (Fig. 2) is a higher power view showing the individual cells, the variation of the size of the cells and the amount of chromatin in the nuclei. The tumor is clearly malignant and the cells certainly remind one of epithelial cells more than any other type. Figure 3A was prepared by Dr. Owen to show a quadruple mitosis. A cell may be seen which is dividing into four parts. In Figure 3B a cell shows a triple mitosis. The finding of mitoses is characteristic of tumors and is one of the criteria for the diagnosis of malignancy. When one finds triple or quadruple mitotic division in the cells collected from pleural fluid or peritoneal fluid, a diagnosis of malignant tumor can be made; normal cells do not show such multiple mitoses. Figure 4 is a section of the tumor stained to

show reticulum. It is seen that the reticulum is associated with the connective tissue and not with the individual cells. Mesotheliomas have reticulum fibers so that this finding makes it possible for us to conclude that the patient had a carcinoma of the apex of

the lung and not a mesothelioma. In Figure 5 there is a section of one of the nodules in the lung. It is seen that in places the tumor fills the alveoli and in other areas it grows directly into the tissues. There is a small amount of necrosis but necrosis is not a con-

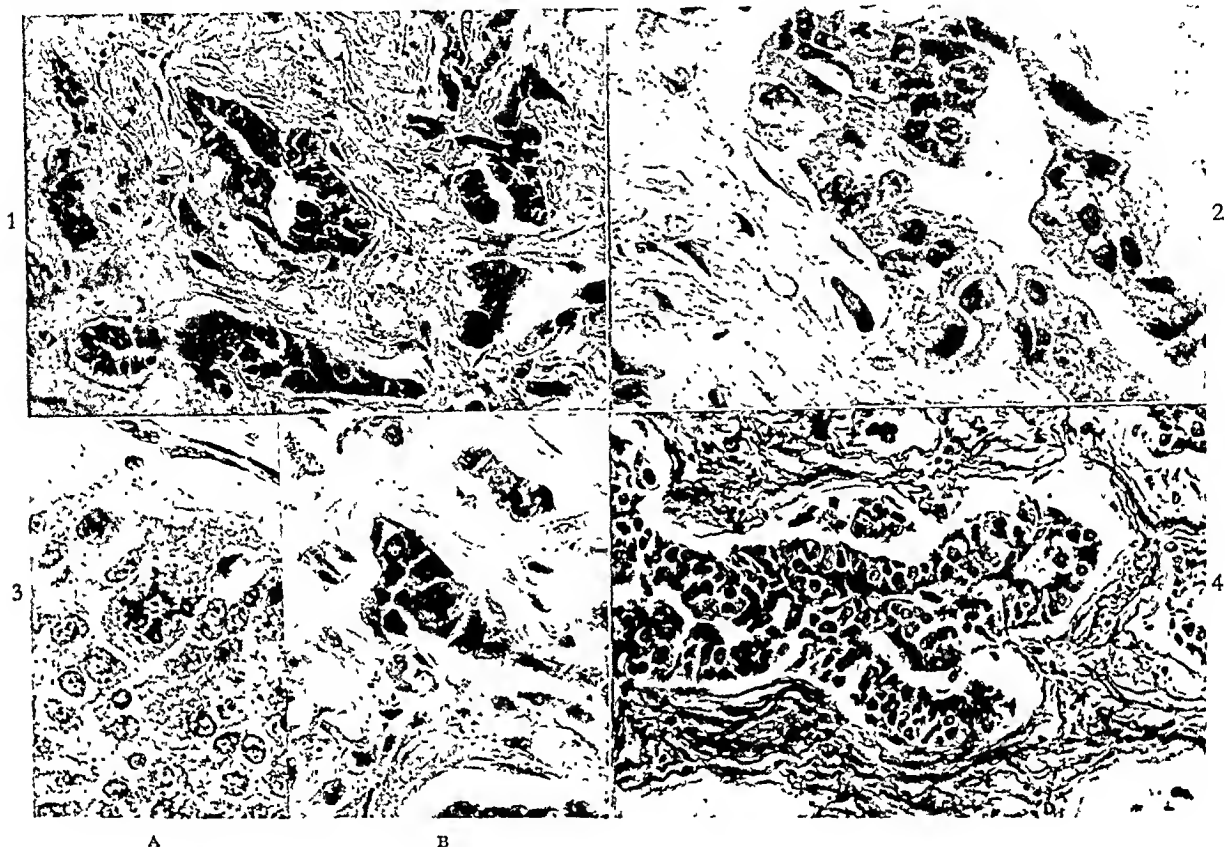


FIG. 1. Section of the pulmonary tumor.

FIG. 2. Another section from the tumor under higher magnification. The histologic appearance is characteristic of a malignant lesion.

FIG. 3. A, section from the tumor showing a quadruple mitosis; B, another area of the tumor in which a triple mitosis is visible.

FIG. 4. A section of the tumor stained to show reticulum.



FIG. 5.

FIG. 6.

FIG. 5. Section through one of the nodules in the lung. Note that some malignant cells are present within the alveoli whereas others have invaded connective tissue itself.

FIG. 6. Section of the metastatic nodule in the cerebellum.

spicuous feature of this tumor. A section through the cerebellum (Fig. 6) shows the identical cell type which allows us to conclude that the mass in the cerebellum is metastatic from the lung. It is of interest that aside from the two nodules in the lung and the nodules in the two tracheobronchial lymph nodes the cerebellar mass represented the only other metastasis. The hemorrhage into the metastatic nodule consists in most part of well preserved red blood cells. In a few areas there are granules of hemosiderin indicating hemorrhage of greater duration than a day or two.

With the anatomic evidence in relation to the clinical history the story may be completed by stating that the patient had a primary carcinoma of the apex of the lung which had metastasized to the cerebellar hemisphere. Over a period of several weeks there was an increase of intracranial pressure giving rise to the signs and symptoms which brought about his hospitalization. Somewhere between twenty-four and forty-eight hours before death, but probably at the time he fell out of bed, a large hemorrhage into the tumor occurred which led to his death. Terminally pulmonary edema occurred.

It might be well to review the diagnostic possibilities, given an undefined intracranial tumor. In a study of a large series of cases it was found that 48 per cent were gliomas, 15 per cent meningeal tumors and 18 per cent metastatic tumors. Seventy-eight to 92 per cent of a series of 114 cases of metastatic brain tumor were not clinically evident. In other words, a diagnosis of a brain tumor was not apparent on the basis of the clinical history and the physical findings. Statistically, in the patient under discussion today there was an 82 per cent chance that the clinical diagnosis would not be sufficiently apparent to allow the neurologists and internists to make a complete diagnosis. These statements are based on the experience of Baker at Duke University Hospital in North Carolina. It is of interest

to consider further that of primary tumors of the lung, 15 per cent metastasize to the brain, whereas 16 per cent of primary breast tumors and 4 per cent of primary prostatic and gastric carcinomas metastasize to the brain. In other words, given a metastatic tumor in the brain the most likely primary site is the breast or the lung. In one study of a series of cases of metastatic tumor in the brain, the primary site was in the lung in 21 per cent, in the breast in 21 per cent, in the gastrointestinal tract in 11 per cent and in the prostate in 1 per cent. In contrast with these figures, the primary site of the tumor when there is no metastasis in the brain is quite different: 7 per cent in the lung, 18 per cent in the breast, 53 per cent in the gastrointestinal tract and 8 per cent in the prostate.

DR. WOOD: I would like to ask Dr. Levy if he believes that every patient who has a brain tumor and is to be operated on should have a chest film?

DR. LEVY: It certainly should be routine.

DR. WOOD: Dr. Jones, what is the explanation for the high spinal fluid pressure?

DR. JONES: It was probably due to the recent hemorrhage into the tumor.

DR. WOOD: Dr. Fletcher should certainly be congratulated on suggesting the correct diagnosis.

Final Anatomic Diagnosis: Carcinoma involving the apical pleurae of the left lung, metastases to the left lung, the bronchopulmonary lymph nodes and parietal pleura on the left, and to the right cerebellar hemisphere; hemorrhage into the right cerebellar hemisphere with encephalomalacia, advanced; cerebellar pressure cone; congestion and edema of the lungs, moderate.

Negative Diagnoses: No histologic changes in the motor area of the brain of the type seen in paresis, no ulcer or scar in stomach or duodenum.

Acknowledgment: Illustrations are from the Department of Illustration, Washington University School of Medicine.

Agranulocytosis in Induced Tertian Malaria*

MAJOR BENJAMIN R. GENDEL, MAJOR MARK M. KROLL and CAPTAIN ALFRED D. LEONE

MEDICAL CORPS, ARMY OF THE UNITED STATES

ON infrequent occasions in the management of a large number of individuals undergoing artificially induced malaria, a profound depression of the granulocytes, in addition to the commonly seen leukopenia, may be encountered. Moore⁷ found three cases of agranulocytosis in 600 patients treated with induced malaria. Meyer,⁶ Jacobson and Abel⁵ and Heldt and Goder⁴ have described five similar cases, two with fatal outcome.

It is of importance that in one of the fatal cases,⁶ the agranulocytosis (white blood count, 2,500, 7 per cent granulocytes) with ulceration of the tongue was noted after the sixth tertian malarial paroxysm but the malaria was not interrupted. Although the exact number of chills that were allowed subsequently was not clearly stated, the blood picture remained essentially unchanged for the ensuing seven days. On the seventh, ninth and eleventh days following the discovery of agranulocytosis blood transfusions were given. The patient died the following day of pulmonary gangrene and bullous dermatitis. Permission for necropsy was not obtained. In the other fatal case⁴ agranulocytosis developed some time between the fifteenth and seventeenth tertian febrile responses. Within twenty-four hours after the seventeenth chill the patient died of pulmonary embarrassment. The outstanding finding at autopsy was a heavy, non-crepitant, dark purple lower lobe of the right lung, which on section, exuded a large amount of reddish fluid. Microscopic examination revealed "large areas of mas-

sive hemorrhage containing almost pure red cells with practically no leukocytic infiltration." In other areas the alveoli were filled with pink fluid. The anatomic diagnosis was general paresis; lobar pneumonia, right lower lobe; old subdural hematoma; splenomegaly; hepatomegaly and hemangioma of the liver.

In none of the papers was an examination of the sternal marrow or postmortem section of the bone marrow mentioned.

In slightly over one hundred military personnel treated with artificially induced tertian or quartan malaria by one of the authors (Dr. Kroll) one instance of agranulocytosis was encountered. It was deemed of interest to present the data in our case, including a report of sternal puncture study. It should be pointed out that the granulocytopenia developed during malaria therapy with no other known granulocytotoxic agent involved.

CASE REPORT

A twenty-eight year old white soldier was admitted March 2, 1945, for evaluation and treatment of neurosyphilis.

The family history and past history were not relevant. The patient denied knowledge of early acquired syphilis. His syphilitic infection was discovered in 1938, when a routine premarital serologic test for syphilis was positive. From 1938 to February, 1943, the patient received approximately fifty arm and fifty hip injections with intervening rest periods. There were no reactions to treatment. In December, 1944, routine blood Kahn and Wassermann tests were positive. The spinal fluid examination in

* From the Medical Service, Lovell General Hospital, Fort Devens, Mass.

December, 1944 revealed 106 white blood cells, positive globulin, Wassermann test positive in 0.1 cc., 0.25 cc., 0.5 cc., 1.0 cc. and a colloidal gold curve of 5554432111.

On admission to this army hospital the patient had no complaints. Symptomologic review of all systems was negative.

The physical examination revealed a medium

mann test anticomplementary in all dilutions and a colloidal gold curve of 5543322100. A complete blood count on March 3, 1945, showed 14.5 Gm. of hemoglobin (Sahli), white blood cells 12,100, 68 per cent segmented forms, 5 per cent stab forms, 2 per cent eosinophiles, 2 per cent monocytes and 23 per cent lymphocytes.

TABLE I

Date	White Blood Cells	Segmented Forms, Per Cent	Juvenile Forms, Per Cent	Stab Forms, Per Cent	Basophiles, Per Cent	Eosinophiles, Per Cent	Monocytes, Per Cent	Lymphocytes, Per Cent
March 29	3,800	9		7			6	78
March 30	3,450	3		1	3		5	88
March 31	4,750	6		1	1		2	91
April 1	4,300	3		2	2		5	89
April 2	4,850	10	2	6		1	4	76
April 4	4,300	20		2			1	76
April 5	5,250	38		2	1	1	3	57
April 6	6,600	32		5		1	3	58
April 7	10,400	41		3			3	52
April 9	7,750	37					3	60
April 12	8,250	34		7		1	2	56
April 16	10,450	50		1		4	1	44
April 23	8,550	40		4		4	2	50

built, well nourished male, 5 feet 7 inches, weighing 155 pounds. The patient was not acutely ill or in any physical distress. Mental response and orientation in all spheres were within normal limits. The abnormal findings were as follows: The right pupil was slightly larger than the left, there was a sear over the urethral meatus and moderate enlargement of postauricular lymph nodes. Aside from the minimal anisocoria there was no clinical evidence of central nervous system disease. Blood pressure was 116/84 and the pulse was 74.

The laboratory data showed that the urinalysis was normal; blood Kahn and Wassermann tests positive; NPN 28 mg. per cent; blood sugar 90 mg. per cent; ieterus index 9; x-ray of heart and lungs and ECG normal. Smears for plasmodia were negative. Spinal fluid examination on March 5, 1945, revealed 196 white blood cells, negative globulin, total protein 20 mg. per cent, Wassermann test anticomplementary in all dilutions and a colloidal gold curve of 554321-0000. A repeat spinal fluid study on March 14, 1945, revealed 61 white blood cells, positive globulin, total protein 16 mg. per cent, Wasser-

During the clinical course a diagnosis of asymptomatic neurosyphilis (Grade III) was made. On March 15, 1945, the patient was inoculated intravenously with 4 cc. of tertian malarial blood. The initial febrile paroxysm occurred on March 17, 1945; thereafter, chills recurred regularly at thirty-three to thirty-six hour intervals. Blood smears revealed *P. vivax*. The white blood count on March 19, 1945, was 7,600, with 58 per cent segmented forms, 2 per cent stab forms, 2 per cent monocytes and 38 per cent lymphocytes. Except for marked weakness, which was not considered unusual, the patient tolerated malaria therapy well. Routine blood counts, performed twice weekly, were within expected limits until March 29, 1945, when at the ninth febrile paroxysm, a precipitous drop in granulocytes was observed. Simultaneously, for the first time slight enlargement of the spleen was detected. A white blood count the next day disclosed a further decline in granulocytes and antimalarial therapy, consisting of 0.2 Gm. of atabrine every six hours for five doses followed by 0.1 Gm. of the drug three times a day for six days, was promptly instituted. Despite the

atabrine barrier the patient broke through on March 31, 1945, with another febrile paroxysm (the tenth). Table 1 demonstrates the serial white blood counts.

On April 1, 1945, the patient complained of a cold, manifested by nasal discharge and dry cough. The physical examination revealed no abnormality of the respiratory tract except a slight redness of the pharynx. As a prophylactic measure, 25,000 units of penicillin were administered intramuscularly every three hours for a total of 850,000 units. The symptoms of upper respiratory infection subsided in a few days and the patient enjoyed an uneventful convalescence from malaria. Mapharsen therapy consisting of 0.06 Gm. twice weekly was instituted five weeks following cessation of malaria. After eight injections of the arsenical, which was tolerated without any untoward clinical or hematologic reaction, the patient was discharged from the hospital.

A specimen of the sternal marrow taken on March 31, 1945, revealed a marrow of normal cellularity. The count of 1,000 marrow cells was as follows: Myeloblasts 2.0 per cent; promyelocytes 4.0 per cent; myelocytes, neutrophilic 33.5 per cent; metamyelocytes, eosinophilic 0.5 per cent; metamyelocytes, neutrophilic 18.5 per cent; neutrophils 3.5 per cent; lymphocytes 10.0 per cent; erythrocytes 0.0 per cent; normoblasts A, 1.0 per cent; normoblasts B, 12.0 per cent; normoblasts C, 9.0 per cent; plasma cells 2.0 per cent and distorted cells 4.0 per cent. Many of the metamyelocytes had poorly differentiated granules. Vacuoles were noted in the cytoplasm and in the nucleus of a number of the myelocytes. Erythropoiesis was normal and an ample number of megakaryocytes were present.

COMMENTS

The question may be raised as to whether the blood picture in this patient represents the leukopenia which commonly accompanies malaria or whether it represents a true agranulocytosis. In our experience with a large number of soldiers suffering from malaria, incurred in both the Mediterranean and Southwest Pacific Theaters of

Operation, and with patients subjected to induced malaria we have not encountered granulocytopenia approaching this magnitude. In addition, the sternal marrow aspiration revealed myeloid cells in normal abundance although mature granulocytes were markedly reduced. This bone marrow picture was found in agranulocytosis by FitzHugh and Krumbhaar² who have interpreted it as a maturation arrest. Moreover, the fatal outcome in the two reported patients indicates that the depression of granulocytes does reach dangerously low levels. The absence of granulocytes in the pneumonic infiltration in one of the reported fatal cases is supporting evidence that this condition is a true agranulocytosis rather than the usual leukopenia of malaria. A similar clinical picture has been observed in kala-azar by Zia and Forkner¹⁰ who also considered that this was "not merely an exaggeration of the usual leukopenia."

The mechanism of the production of this condition is obscure in our patient. In several previously reported cases the issue was complicated by the administration of drugs prior to discovery of the blood picture; however, in others no drugs were administered and none were administered to our patient. It appears reasonable to presume that malaria is capable of acting on the bone marrow to produce an alarming paucity of peripheral granulocytes. This deleterious effect may occur late in the course of induced malaria, as in our patient, or early as described by Jacobson and Abel.⁵

The case of agranulocytosis reported by Franks and Davis³ may possibly represent agranulocytosis occurring after the second malarial paroxysm. These authors attributed the agranulocytosis to quinine, because of an increase in the percentage of granulocytes after discontinuing the medication. However, scrutiny of their data revealed that although the percentage of granulocytes did not increase until quinine was

discontinued, the total white count had been increasing for the preceding week and consequently the absolute number of granulocytes had risen from 391 to 960 before quinine was discontinued. This would tend to cast doubt on the etiologic rôle of quinine, especially if the mechanism of production of the agranulocytosis is assumed to be a hypersensitivity, as in agranulocytosis secondary to amidopyrine. Recently, the theory of hypersensitivity has been further complicated by the observation of Nixon, *et al.*,⁸ who demonstrated that if sulfadiazine were continued in patients who developed agranulocytosis presumably secondary to the sulfadiazine these patients continued to recover. A similar phenomenon occurring with thiouracil was reported recently by Williams and Clute.⁹ This would indicate that hypersensitivity was not the only factor in the development of the condition but that it developed in some other way.

The possibility of the occurrence of agranulocytosis in the course of induced malaria must be borne in mind constantly. In the event that the condition is detected it is important to terminate the malaria promptly. To prevent septic complications it is advisable to administer penicillin.¹

SUMMARY

A case of agranulocytosis occurring during the course of induced tertian malaria is presented. The patient received no granulocytotoxic drugs. Recovery followed prompt termination of the malaria by atabrine.

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Editorial

Nitrogen Mustard Therapy

THE leukopenia following exposure to mustard gas which Krumbhaar¹ described in 1919 attracted little interest. The nitrogen mustards of World War II, on the other hand, received considerable attention. It was demonstrated that the biological effects of these compounds parallel and are in many respects identical with those of roentgen rays.² A cytotoxic effect is produced which is closely related to the proliferative activity of tissues and this is particularly marked upon the hemopoietic tissue. A logical outcome of these investigations has been the clinical trial of certain of the nitrogen mustards in cases of neoplastic disease, especially the malignant processes involving chiefly the lymph nodes and bone marrow.

The action of the mustards depends upon intramolecular cyclization with the formation of a series of ethylene imonium compounds. The latter are highly reactive and are capable of alkylating a large number of biologically functional groups such as sulfhydryl, carboxyl and many others. The cytotoxic action probably is the result of the inactivation of one or more cellular enzymes.

Even minimally effective doses produce a striking inhibition of mitosis. Resting cells and cells in active mitosis are not apprecia-

bly affected but cells in the premitotic phase are arrested at that stage. Larger doses lead to nuclear fragmentation and dispersal of chromatin.³ There is no evidence that there is a difference in the toxicity for malignant as opposed to normal tissue. Nevertheless, the mustards, especially methyl bis (β -chloroethyl) amine hydrochloride (HN_2), appear to be useful therapeutic agents.

Promising results have been observed in Hodgkin's disease, lymphosarcoma, chronic myelocytic and chronic lymphocytic leukemia and in polycythemia rubra vera.⁴⁻⁸

³ FRIEDENWALD, J. S., BUSCHKE, W., SCHOLZ, R. O. and MOSES, S. G. Some effects of sulfur and nitrogen mustards on cell nuclei in mammalian cornea. Approaches to tumor chemotherapy. American Association for the Advancement of Science, p. 358. Washington, D.C., 1947.

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⁷ ApTHOMAS, M. I. R. and CULLUMBINE, H. Nitrogen mustards in Hodgkin's disease. *Lancet*, 1: 899, 1947.

⁸ WINTROBE, M. M., HUGULEY, C. M., JR., McLENNAN, M. T. and LIMA, L. P. C. Nitrogen mustard as a therapeutic agent in Hodgkin's disease, lymphosarcoma, and leukemia. *Ann. Int. Med.*, 27: 529, 1947.

¹ KRUMBHAAR, E. B. Role of the blood and the bone marrow in certain forms of gas poisoning. *J. A. M. A.*, 72: 39, 1919.

² GILMAN, A. and PHILIPS, F. S. The biological actions and therapeutic applications of the β -chloroethyl amines and sulphides. *Science*, 103: 409, 1946.

The results in the first of these have been particularly impressive. The effect on the fever is pronounced and reduction in the size of enlarged lymph nodes and spleen, relief of symptoms due to pressure and a general sense of well being follow therapy. In a number of subjects "resistant" to x-ray therapy, remissions have been induced by nitrogen mustard therapy. It is not clear whether the remissions following treatment with HN_2 are as long as those which may be observed after roentgen therapy. Some hold that nitrogen mustard should be reserved for those patients in whom systemic involvement is extensive, local involvement being best treated by roentgen therapy. Whatever the final answer to these unsettled points may be, there can be no doubt that the introduction of the nitrogen mustards represents a therapeutic advance in the management of Hodgkin's disease. For the treatment of this disease, HN_2 is clearly superior to radioactive phosphorus.⁹

There is no good evidence that nitrogen mustard is more effective in the treatment of the lymphosarcomas or the leukemias than is roentgen therapy. It has been found, however, that HN_2 is a useful agent for the management of these disorders and the drug compares favorably with other available forms of treatment. It is perhaps but a matter of availability or convenience whether roentgen therapy or nitrogen mustard is used in a given case. Urethane is still too new for a comparison to be made. No study has been reported in which one of the radioactive isotopes has been compared with HN_2 but what evidence there is suggests that the latter may be the superior therapeutic agent. As to the acute leukemias, the best that can be said is that only very temporary alterations have been produced by the use of nitrogen mustard. Relief of

bone pain has been helpful in some instances, however.

Although extensive cellular damage may be produced by the nitrogen mustards if large enough doses are given, the amounts used therapeutically (0.1 mg. per Kg. body weight, repeated three to six times in a course) produce evidence of toxic effects only in two systems, the gastrointestinal and the hemopoietic. Nausea and vomiting almost invariably follow the first injections of each course. The intensity of these symptoms varies greatly. As compared with similar symptoms accompanying roentgen therapy, their duration is often more brief even though their severity may be greater.

A reduction in the leukocyte count is frequently encountered with nitrogen mustard therapy. Both granulocytes and lymphocytes are affected. There may be a variable decrease in red cells as well as in platelets. Care must be taken to prevent the development of the agranulocytic syndrome and serious bleeding can occur although both of these complications have been quite rare. Recovery from these effects on the blood occurs in three or four weeks. Anemia, if present prior to therapy, has been relieved in those subjects responding favorably to therapy. Thus in chronic leukemia a fall in the leukocyte count has often been followed by a decrease in anemia or its complete disappearance.

Of chief importance in relation to the introduction of the nitrogen mustards, however, is the fact that an almost infinite variety of beta-halogenated amines can be prepared. Consequently, the discovery of chemical agents which possess an action like that of roentgen rays offers hope that compounds can be devised which will have a selective action on neoplastic tissue and yet will produce relatively little damage to normal tissue.

MAXWELL M. WINTROBE, M.D.

⁹ REINHARD, E. H., MOORE, C. V., BIERBAUM, O. S. and MOORE, S. Radioactive phosphorus as a therapeutic agent. *J. Lab. & Clin. Med.*, 31: 107, 1946.

Endocrine Changes Associated with Laennec's Cirrhosis of the Liver*

CHARLES W. LLOYD, M.D. and ROBERT H. WILLIAMS, M.D.

Boston, Massachusetts

ALTHOUGH many papers have been written on cirrhosis of the liver, not much attention has been given to the not uncommonly associated endocrine changes, chief of which are gynecomastia, atrophy of the testes, menstrual disturbances, sterility, impotence and decrease in axillary hair. The results of investigations of the rôle of the liver in steroid metabolism and the endocrine disturbances in cirrhosis of the liver may therefore be of interest. Seventy-one unselected patients with Laennec's cirrhosis of the liver were studied with particular reference to endocrine abnormalities.

REVIEW OF CLINICAL STUDIES

Silvestrini^{1,2} first reported gynecomastia and Corda³ first described testicular atrophy associated with cirrhosis, so that the triad of gynecomastia, testicular atrophy and Laennec's cirrhosis is sometimes referred to as "The Silvestrini-Corda Syndrome." Eppinger⁴ added loss of axillary hair to this triad. Jacob⁵ considered this latter change so characteristic of cirrhosis of the liver that he hesitated to make the diagnosis in its absence.

Impotence and loss of libido have been found by Eppinger,⁶ Ratnoff and Patek⁷ and Bean⁸ to be present not infrequently in males with cirrhosis of the liver.

The vascular arterial "spider" may be the result of endocrine changes since Bean⁹ has been able to produce "spiders" by the administration of estrogen.

Changes in the menstrual pattern have been observed by Rolleston,¹⁰ Paiseau and Oumansky,¹¹ Ratnoff and Patek,⁷ Laignal-Lavastine, Troisier and Boquien,¹² Bean,⁸ Hartwell-Johnson.¹³ These changes usually consist of menorrhagia, postmenopausal bleeding and occasionally amenorrhea.

Silvestrini¹ first explained gynecomastia associated with cirrhosis as being due to an increased collateral circulation through the breast or to abnormal substances which were not removed from the blood stream by the damaged liver. Del Guerra¹⁴ agreed with this view. Corda³ believed that an endocrine imbalance was the cause of gynecomastia and testicular atrophy. Silvestrini² later suggested that the breast changes were not true gynecomastia, but rather a chronic inflammation, at least in some cases. The hypotheses of Bolaffi,¹⁵ Cioni¹⁶ and Pellegrini¹⁷ are in accord with this.

Boccia¹⁸ believed that alcohol had a specific toxic effect on the testes and that those patients with gynecomastia and testicular atrophy have a latent hereditary predisposition to hermaphroditism which becomes apparent when unknown circulating substances depress the masculine elements in their endocrine system. Boccia,¹⁸ as well as Pende,¹⁹ Paula,²⁰ D'Antona,²¹ Tobler,²² Zanalda²³ and Manai²⁴ believed that testicular failure was the primary cause of gynecomastia.

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

Riebler²⁵ has advanced the novel theory that ingestion by individuals with chronic alcoholism of large quantities of milk, a supposedly feminine substance, is an etiologic agent in gynecomastia. Menville²⁶ suggested that gynecomastia in patients with cirrhosis may be due to a cerebral lesion and that these patients represent mild cases of Wilson's disease (tetanoid chorea). Paula¹⁹ also considered that the nervous system may be implicated, perhaps through involvement of the nervous factors controlling sexual processes.

Edmondson, Glass and Soll^{27,28,29} have offered a more satisfactory explanation of gynecomastia which is based on the observation that breast changes are similar to those which follow experimental estrogen stimulation. Eight of fourteen men with cirrhosis had gynecomastia and were found to excrete large amounts of free and small quantities of conjugated estrogens.^{27,28} They also had low urinary androgen excretions. Approximately 85 per cent of estrogen injected into patients with cirrhosis was recovered. In three patients most of the urinary estrogen was conjugated but in the fourth, who had more severe liver failure, the estrogen was mainly in a free form.²⁹

Gilder and Hoagland³⁰ have recently studied estrogen excretion in young men suffering from acute infectious hepatitis. These authors found that during the phase of greatest liver damage there was an increased urinary excretion of estrogen and a decrease of ketosteroids. Recovery from this liver disease was followed by a return to normal of the urinary excretion of these steroids. Menstrual disorders have also been observed in female patients with infectious hepatitis.³¹

Testicular atrophy was found at autopsy by Morrione³² in 57 per cent of twenty-eight patients with cirrhosis. He concluded that long-standing liver damage is necessary to produce this change and that the amount of atrophy is roughly proportional to the extent of liver damage. Experimental confirmation of these autopsy findings was obtained by production of

much more severe testicular damage following estrogen administration to rats with damaged livers than in normal animals. A depression of the function of normal testes by estrogens has been demonstrated.^{33,34}

Wu³⁵ found decreased involution and nodular hyperplasia of the prostate in ten of eleven men who died of cirrhosis, whereas in the same age group only 50.5 per cent of the patients who died from other causes exhibited these changes. Metaplasia of the urethral epithelium similar to that produced in rats by estrogen administration was also seen.

A few studies of pathologic changes in the entire endocrine system have been made. Barrelet³⁶ found testicular atrophy in 78 per cent of male patients with cirrhosis. He observed no characteristic changes in the ovaries, adrenals or pancreas of female patients. Seventy-nine per cent of his patients showed a basophilic granulation of the thyroid colloid; a decrease in size of the thyroid gland was present in 31 per cent. No constant changes could be seen in the pituitary glands. Although 28 per cent had an increase in the basophilic cells, 25 per cent had an increase in chromophobe cells. Fittipaldi³⁷ reported lesions similar to those seen by Barrelet and also described pancreatic changes. This author suggested that these abnormalities were due to coincidental disease and were not related to the cirrhosis. In a case of cirrhosis with gynecomastia, Capriglione, Berardinelli and daCosta Cruz³⁸ found a considerably increased number of basophil cells in the pituitary. Boecia¹⁸ reported testicular atrophy and decreased function of the adrenal glands.

Many studies indicate that the liver plays an important rôle in the normal organism in the intermediate metabolism of the sex steroids. Some of the results are reviewed in the following section.

REVIEW OF ANIMAL STUDIES

Only a very small proportion of estrogen injected into the rat could be recovered from the urine, feces or carcass by Dingemans

and Laqueur.³⁹ This suggested the presence in the body of a very efficient mechanism for destroying or inactivating estrogen. Evans and Burr⁴⁰ demonstrated that less estrogenic effect was produced by the intraperitoneal injection of ovarian hormones than by subcutaneous injection. Silberstein, Engel and Molnar⁴¹ and Zondek⁴² showed that liver inactivates estrogen *in vitro*.

Parker and Tenny⁴³ found more estrogen in human maternal and fetal livers than in any other tissue. They were unable to demonstrate a significant increase in the estrogen content of cirrhotic livers.⁴⁴

Many studies have indicated that the liver inactivates estrogen. Perfusion of the heart-lung and heart-lung-liver preparations has demonstrated that the greatest destruction of estrogen occurred when the perfusate passed through the liver.⁴⁵ One frequently used experimental technic has been the comparison of the effects on the genital organs of estrogens which have circulated through the liver with the effects of estrogens which have by-passed the portal circulation.⁴⁶⁻⁶⁰ From these data it can be concluded that synthetic as well as naturally occurring estrogens are inactivated by the liver *in vivo* although the former are not inactivated as rapidly as the latter. Zondek and Sklow⁶¹ have demonstrated that this function is not influenced by the reticulo-endothelial system.

In vitro technics have also demonstrated inactivation of estrogens by the liver. Shaking with liver pulp inactivates natural^{41,42} and synthetic estrogens,⁶² although twice as much liver is required to inactivate diethylstilbestrol as to inactivate estrone. Twombly and Taylor⁶³ report that human liver slices do not have as marked capacity to inactivate estrogens as do slices of rat liver. No correlation was found between the estrogen inactivating ability of the liver and the presence or absence of cancer. Heller⁶⁴ has demonstrated that inactivation of estrogen by liver slices depends upon at least two enzyme systems. Estradiol (dihydroxyestrin) is reduced to an estrogen having the activity of estriol (the trihydroxy form). Addition of cyanide to the medium prevents this action

presumably through poisoning of an oxidative enzyme. Estrone is also changed by liver slices to an estrogen having the activity of estriol. Addition of cyanide results in the formation of an estrogen similar in activity to estradiol. It would seem, therefore, that a reducing enzyme system causes the conversion of estrone to estradiol and that an oxidative system changes this more potent estrogen to the less potent trihydroxy form, estriol. This work is in agreement with the finding by Segaloff⁵³ that the point of attack seems to be the OH group, since substitution of this group affords partial protection against inactivation. Schiller and Pincus^{65,66} have perfused rat organs with estrogens and have reached the conclusion that estradiol and estrone are interconvertible and both can be excreted as estriol. This is the generally accepted hypothesis concerning the path of estrogen metabolism in the human.⁶⁷

Injury of the liver by poisoning with carbon tetrachloride,^{68,69} or partial hepatectomy,⁷⁰ results in a decreased ability of the liver to inactivate estrogen. Production of liver injury by dietary deficiency has led to the study of the effects of diet on estrogen metabolism. Estrogen therapy in the human has been reported to increase the need for the vitamin B complex⁷¹ or to decrease its utilization.

Dietary deficiency decreases the ability of the liver to inactivate either endogenous or exogenous estrogens. Biskind and Biskind⁷²⁻⁷⁴ have reported decreased inactivation in animals deficient in the vitamin B complex, specifically riboflavin and thiamine. This work has been confirmed by Segaloff and Segaloff⁷⁵ who also found that these vitamin deficiencies caused a reduction in response to subcutaneously injected estrogen, presumably due to end-organ refractoriness. Shipley and Gyorgy⁷⁶ found that yeast corrected the decreased ability to inactivate estrogen in animals with liver injury resulting from a protein-deficient diet. However, the paired feeding experiments of Drill and Pfeiffer⁷⁷ showed that a comparable degree of inanition in rats receiving plenty of vitamin B complex resulted in a decrease of the

ability of the liver to inactivate estrogens commensurate with that found in animals on vitamin B deficient diets.

Singher et al.^{78,79} demonstrated that defective inactivation of estrogen resulting from riboflavin and thiamine deficiency could be corrected by methionine. These authors suggested that a direct relationship exists between dietary protein intake and riboflavin storage. Liberal amounts of dietary riboflavin were not retained when the protein intake was low.

Decreased ability to inactivate estrogens has recently been used to estimate liver injury due to dietary deficiency in experimental animals.⁸⁰ Clinical application of the relation of vitamin deficiency to decreased estrogen inactivation has been made by Biskind, Biskind and Biskind,^{81,82} who have reported improvement with B vitamin complex therapy in disorders possibly due to excessive estrogenic activity resulting from inadequate inactivation. Ayre and Bauld⁸³ have described changes in the estrogen metabolism and vitamin excretion of female patients with carcinoma and functional uterine bleeding.

Androgens have also been shown to be inactivated by the liver and vitamin B deficiency was not found to decrease this effect.^{57,84,85}

The work reviewed so far has dealt with the "inactivation" of estrogens by the liver. "Inactivation" by the liver is not the only means by which steroid hormones are removed from the circulation. Longwell and McKee⁸⁶ showed that following injection of estrone into dogs, estrogen of a different type, non-ketonic, was recoverable from the bile. Cantarow, Pasehki, Rakoff and associates⁸⁷⁻⁹¹ have also recovered estrogen and androgen from bile. They state that biliary excretion is the avenue of egress from the body and that the liver does not "inactivate" estrogen. Emery and Joyce⁹² found that severance of the bile ducts increased the duration of effect of diethylstilbestrol and estrone. Morrione⁹² reported less damage to the testes of the rats receiving estrogen when the bile ducts were ligated than when the

liver was injured by carbon tetrachloride. He believed, therefore, that failure of inactivation of estrogens was more important than decreased excretion in the bile in causing testicular atrophy.

The possibility that estrogens may influence the course of liver injury must be considered. Although Roberts et al.⁹³ were not able to demonstrate any changes in glycogen, fat, or nitrogen in the livers of normal dogs receiving diethylstilbestrol or estradiol, Taurog⁹⁴ and co-workers reported that diethylstilbestrol increases the incorporation of inorganic phosphorus into phospholipid in the liver. Allen's⁹⁵ observation that administration of estrogen plus progesterone induces an increased number of binucleated cells in the rabbit liver, whereas castration decreases them, suggests that the high steroid level in patients with cirrhosis may influence repair of the liver.

Szego and Roberts⁹⁶ reported that approximately two-thirds of the circulating blood estrogen is bound to protein. In view of this observation, the marked abnormalities of protein formation and metabolism seen in hepatic cirrhosis may be considered as contributing to the alteration of estrogen metabolism observed in these patients.

PLAN OF STUDY

Patients with cirrhosis of the liver, diagnosed by history, physical examination and laboratory tests, were examined for changes in endocrine function.

In most of the patients estimations were made on the serum or plasma of the icterus index, cephalin flocculation, formol gel, total protein and prothrombin. In many of the patients urine urobilinogen, serum bilirubin and serum albumin and globulin levels and thymol turbidity and broinsulphthalein retention tests were done. For the latter test 5 mg. of the dye per Kg. of body weight was administered and the amount of dye in the serum was estimated at five- and forty-five-minute intervals thereafter. Alkaline phosphatase concentrations were occasionally determined.

The history, physical findings, laboratory data and clinical course have been reviewed by Dr. Franklin White who has classified the cirrhosis into three groups: (1) "mild," (2) "moderate,"

(3) "severe." The clinical impressions of the observer, of which Dr. White was ignorant when he reviewed the data, agreed closely with his classification.*

The endocrine changes searched for were abnormalities in libido, potency, body hair,

in testicular size and turgor were associated with a decreased function of the seminiferous tubules.

Gynecomastia was considered to be present when there was felt a firm disc of tissue with well demarcated borders and a centrally placed nipple. Cords of glandular elements could often

TABLE I

SUMMARY OF ENDOCRINE CHANGES IN FORTY-SIX MALES WITH CIRRHOSIS OF GRADE III SEVERITY

Age	No. of Cases	Decrease of Libido*				No Change in Libido Libido Never Good	Decrease of Body Hair†				Gynecomastia‡				Testicular Atrophy Testes Normal	Spider Telangiectasis	Testicular Atrophy and Gynecomastia	Testicular Atrophy without Gynecomastia	Gynecomastia without Testicular Atrophy	Testes No mal and No Gynecomastia	Gynecomastia and De- crease Axillary Hair	Decrease Axillary Hair without Gynecomastia	Normal Axillary Hair and No Gynecomastia	Gynecomastia with De- crease Axillary Hair		
		+	++	+++	++++		+	++	+++	++++	+	++	+++	++++												
20 to 29	1								1																	
30 to 39	2					1	1		1					1					1	1	1	1				
40 to 49	21	2	4	3	5	2	4	9	5	2	3	6		1	2	13	5	16	6	10	3	2	9	1		
50 to 59	15	1	8	2	2	1	1	2	8		2	4		1	3	12	1	12	7	7	1	6	10	2		
60 to 69	5	1	1			2	1	1	1	1	2	2			1	4	1	5	3	1	3	2	2			
70+.	2				2						2					2		1				2		2		
Total	46	4	13	5	9	4	8	12	16	3	9	12		2	7	31	10	37	16§	20	5	5	19	21	4	2

* + slight decrease of libido
++ moderate decrease of libido
+++ severe decrease of libido

++++ complete loss of libido

† + 25% loss of body hair

++ 50% loss of body hair

+++ 75% loss of body hair

++++ 100% loss of body hair

‡ + slight unilateral gynecomastia

++ moderate unilateral gynecomastia

+++ marked unilateral gynecomastia

++++ bilateral gynecomastia.

§ 2 of these patients had testes which could not be measured because of edema of scrotum

|| 3 of these patients had testes which could not be measured because of edema of scrotum

breast development, menses, prostatic size and testicular size. The frequency and severity of some of these changes are shown in Table I. In males with testicular atrophy spermatozoa counts were attempted during part of the study but because of the complete loss of libido and potency as well as lack of cooperation, it was soon found that it was almost impossible to obtain seminal specimens. However, enough samples were obtained to indicate that decreases

be made out in this hyperplastic tissue. In a few cases the physical findings were checked by biopsy; in no instance did the histologic finding fail to reveal gynecomastia. Criteria for histologic diagnosis of gynecomastia were those given by Karsner.⁹⁷ Typical biopsy sections are reproduced in the photomicrographs in Figures 1 and 2. The amount of gynecomastia was roughly graded into four groups as shown in Table I: group +, slight unilateral hyperplasia; group ++, moderate unilateral hyperplasia; group +++, marked unilateral hyperplasia; group +++++, bilateral hyperplasia.

Axillary hair loss was estimated on a + to +++++ basis, with + representing up to 25 per cent loss, ++ 50 per cent loss, +++ 75 per cent loss and +++++ 100 per cent loss. In fifteen patients the axillary hair was shaved and weighed and clinical estimation of hair loss was found to be accurate. In none of the males whose axillary hair was called normal was excessive body hair found and almost every one of the

* The three grades of cirrhosis were characterized by the following features: (1) *Mild*—No ascites; no definite icterus, bromsulphthalein less than 20 per cent after forty-five minutes; cephalin flocculation less than 2+. (2) *Moderate*—Icterus (spider telangiectases); collateral portal circulation; moderate amount of urobilinogen in urine; low serum protein; bromsulphthalein 20 to 40 per cent retention; cephalin flocculation 3+ or more; formol gel 2+ or more, no ascites. (3) *Severe*—Ascites (all cases); bleeding; delirium; coma; splenomegaly; icterus index 50+; low serum protein; bromsulphthalein more than 40 per cent retention; cephalin flocculation 4+; formol gel more than 3+.

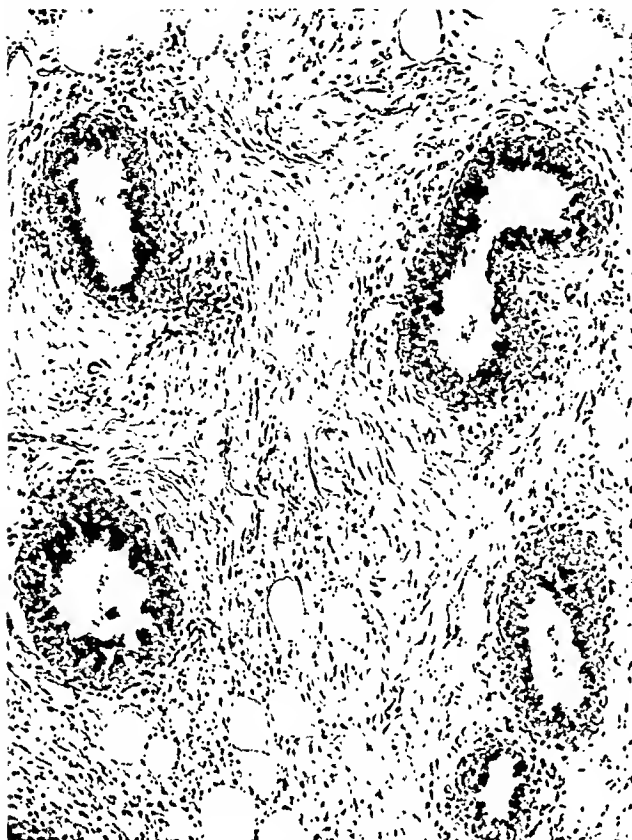


FIG. 1. Photomicrograph of the breast of a male patient, aged forty-four, with grade II cirrhosis and bilateral gynecomastia. Note marked hyperplasia of duct epithelium as well as evidence of stimulation of interstitial tissue.



FIG. 2. Photomicrograph of the breast of a male patient, aged forty-two, with grade III cirrhosis and bilateral gynecomastia. Following testosterone propionate as well as adequate dietary therapy for the liver disease, gynecomastia completely disappeared.

patients stated that he had never had much body hair.

Testicular size was determined in three dimensions. Testes under 4.5 by 2.5 by 2.5 cm. were considered decreased in size. The normal measurements for testes cited in Gray's Anatomy⁹⁸ are 4 to 5 cm. by 2.5 cm. by 3 cm. Since the thickness of the serotum is also included in our measurements, we have made our lower limits of normal slightly higher than those given for the uncovered testis. The testes of ten normal males all had greater dimensions than the above figures.

Estimations of the size of the prostate varied considerably so that these figures are not very satisfactory. However, it can be said that the size was comparable to that of similar age groups of individuals without cirrhosis.

The breasts of all female patients were carefully examined for nodules and an estimation of the amount of glandular tissue was made.

Careful menstrual histories were taken of all

women. Two patients in the reproductive age group had endometrial biopsies.

RESULTS IN MALES

Libido and Potency. Of two patients with grade I cirrhosis, one had a definite but slight decrease in libido. The other had always had a subnormal libido and had noted no change with the development of cirrhosis. Neither patient reported any change in potency.

Five of seven patients with grade II cirrhosis had a marked decrease in libido and two of the five had decreased potency. One patient had never had much libido and he could notice no change. The seventh had normal libido and potency.

A total of forty-six patients with grade III cirrhosis were seen, but only forty-three of these could respond to questioning as three

were comatose. Thirty-one of these, or 72 per cent, had definitely decreased libido and potency. Four patients (9 per cent) had noted no change and eight (18 per cent) had never had normal sexual drive.

Decrease in libido was frequently the first symptom noted by patients with cirrhosis.

Body Hair. One of the two patients with grade I cirrhosis had a 50 per cent decrease in axillary hair, but the other one had no change.

Of the seven patients with grade II cirrhosis five had decreased axillary hair. Normal body hair was present in two.

Forty of the forty-six patients with grade III cirrhosis (87 per cent) had decreased axillary hair, but the other six patients had no change in this regard.

The decrease in axillary hair in the patients with grade III cirrhosis was of a more marked degree than in the other two groups. None of the nine individuals with grade I and II cirrhosis had ++++ hair loss and only two had +++ hair loss. Of the forty-six subjects with grade III cirrhosis the hair loss of nine was classified as ++++ and of three as +++.

Testicular Atrophy. Neither of the two patients with grade I cirrhosis had testicular atrophy.

Five of the seven subjects with grade II cirrhosis had definite testicular atrophy. Although the greatest atrophy was found in a man of seventy, atrophy was also present in four of five men under forty-two years of age.

Of the forty-six subjects with grade III cirrhosis, five had such massive scrotal edema that an accurate estimation of testicular size could not be made. Thirty-one (75 per cent) of the remaining forty-one had definite testicular atrophy. The incidence of atrophy increased *pari passu* with age; no atrophy occurred in three patients under forty years of age, but it occurred in 62 per cent of twenty-one patients in the group aged forty to forty-nine, in 80 per cent of fifteen subjects in the group aged fifty to fifty-four years and in 86 per cent of seven patients over sixty years of age.

Association of Testicular Atrophy with Axillary Hair Loss. Twenty-seven of thirty-one patients (87 per cent) with testicular atrophy had decreased axillary hair. No correlation could be found between the amount of hair loss and the degree of atrophy. Four of thirty-one patients (13 per cent) with testicular atrophy had little, if any, change in axillary hair. Conversely, of forty patients with hair loss, eight (20 per cent) had no change in the size of the testes. All five of the patients on whom no measurements were possible because of scrotal edema had decreased axillary hair.

Gynecomastia. Twenty-three of fifty-five male patients (42 per cent) had gynecomastia. In two patients with mild, or group I cirrhosis, no gynecomastia occurred. Of seven patients with group II cirrhosis there were three subjects with gynecomastia. Two of these were graded + and one was ++++. (Fig. 2.)

Twenty of forty-six patients with grade III cirrhosis had gynecomastia. Twelve of these were classified as +, two as +++ and seven as ++++. One additional patient with grade III cirrhosis was found to have had definite gynecomastia two years previously. At that time he had severe liver decompensation with ascites and icterus. In association with a regimen of high vitamin and high caloric diet and abstinence from alcohol the gynecomastia disappeared.

One of the patients with ++++ gynecomastia developed this condition while he was in the hospital three months after being admitted in cholemic coma. A photomicrograph of one breast biopsy is shown in Figure 1. Following biopsy, the patient was given testosterone propionate in oil intramuscularly, 75mg. per week for two months. During this interval the patient received the usual form of therapy, i.e., high caloric, high protein, high vitamin diet and he made a good recovery with disappearance of ascites and icterus. A subsequent biopsy of the breast showed subsidence of the gynecomastia and later physical examinations revealed normal breasts. This patient had not had any libido for several months and he

developed none during the time that he received testosterone. Four months after the last injection of testosterone, when the patient's general condition was excellent, he noted a slight return of libido but diminished potency persisted. The spermatozoa count at this time was 7,000,000 per cc. with a total count of 14,000,000. Only 45 per cent of the spermatozoa were motile.

Association of Gynecomastia with Other Endocrine Changes. In twenty-one of twenty-three patients with gynecomastia there was a definite decrease in axillary hair. The patient who is reported as having had gynecomastia on a previous admission, but whose breasts were normal following several years of good liver compensation, also had decreased axillary hair.

Definite testicular atrophy was present in sixteen of twenty-one patients with gynecomastia (76 per cent) in whom the testes could be measured. In two other patients with gynecomastia the testes could not be measured due to scrotal edema. Five (24 per cent) of the patients with gynecomastia were not thought to have testicular atrophy.

All but one of twenty-three patients with gynecomastia had decreased libido.

Androgen and 17-ketosteroid Excretion. Four male patients with severe (grade III) cirrhosis were studied for alterations in androgen and 17-ketosteroid excretion. The free and combined 17-ketosteroids excreted in complete pooled three-day urine collections were determined. The urine was extracted with carbon tetrachloride. The extract was purified with Girard reagent and the amount of color formed with metadinitrobenzene was measured. Free and total androgen excretion was determined by the method of Rakoff, Paschkis and Cantarow,⁹⁹ using the comb weight changes in the chick following application once daily for seven days of an ether solution of the androgen to the comb. The androgen assay results are not considered as absolute but are reported simply because they indicate a trend.

After a three-day control period, each patient received 50 mg. intramuscularly of testosterone propionate, following which

another three-day complete urine collection was assayed for 17-ketosteroids and androgens. As can be seen in Table II only a small amount of 17-ketosteroids was excreted before injection of testosterone and there was no increase after injection. No free androgen

TABLE II
AVERAGE TWENTY-FOUR-HOUR URINARY ANDROGEN AND 17-KETOSTEROID EXCRETION FOR THREE-DAY PERIODS BEFORE AND AFTER THE INJECTION OF 50 MG. OF TESTOSTERONE PROPIONATE (EXPRESSED AS MG. OF ANDROSTERONE)

Before				After		
Cirrhosis of the Liver						
	Andro- gen	17-ks. Free	17-ks. Total	Andro- gen	17-ks. Free	17-ks. Total
V.....	10	.36	2.8	0	.29	2.6
G.....	3.9	0	.61	32.3	.64	3.9
B.....	22.2	.26	1.5	59.3	.402	3.8
M.....	46	0	5.6	54.2	.025	5.8
Carcinoma of Common Bile Duct with Biliary Fistula						
Bile....	0	0		
Urine..	6.5	46.3		

was detectable in any of the specimens assayed; therefore only the total androgen values are tabulated.

The increase of androgenic activity and failure of increase of 17-ketosteroids following injection of testosterone is at variance with results reported for normal males¹⁰⁰ in whom from 14 to 70 per cent of the testosterone injected has been recovered from the urine as 17-ketosteroids.

In Table II is also shown the amount of androgen excreted in bile and urine after 50 mg. of testosterone propionate was administered to a woman, age seventy-two, with carcinoma of the bile duct and a biliary fistula. This patient was icteric but had normal cephalin flocculation test, prothrombin time and serum protein level. The serum alkaline phosphatase level was elevated. Very little biliary excretion of 17-ketosteroids or of steroids having androgenic ac-

tivity was found but a considerable increase in urinary androgen excretion occurred following injection of testosterone. In this patient the small amount of androgen excreted in the bile was perhaps due to impairment of liver function indicated by the

RESULTS IN FEMALES

Sixteen female patients with cirrhosis are included in this series. Four of these patients, one in group II and three in group III, had been oöphorectomized many years before the development of cirrhosis. These patients

TABLE III
SUMMARY OF CHANGES IN SIXTEEN FEMALE PATIENTS WITH CIRRHOSIS

Grade of Cirrhosis	Age	No. of Cases	Amenorrhea	Menstrual Change			Decrease in Axillary Hair				Breast Changes		Pelvic Changes	
				Cyclic Decreased Flow	Menometrorrhagia	Irregular Bleeding, Infrequent, Normal Flow	+	++	+++	++++	Atrophy	Nodules	Atrophy	Enlargement of Uterus
I	51	1	1	1	1
II	28
	40†	2	..	1	1	1
	38	1	1	1
III	32-38	4	2	1	..	1	2	1	..	1
	41-45	4	2	..	1	1	1	1	..	2	3	..	2	..
	47-50*	3	3	2	1	3	1
	78	1	1	1	1	..	1	..
Total.....	16	6	1	3	3	4	2	..	5	12	1	3	10

* These patients had had an oöphorectomy.

† This patient had hirsutism.

elevated serum alkaline phosphatase. If this be the case, the ability of the liver to excrete steroid substances in the bile must be extremely sensitive to minor derangements of liver function since this patient had changes in liver function of insufficient severity to cause alteration in the cephalin flocculation test, the prothrombin time or the serum proteins.

Gonadotrophin Excretion. In three male patients with cirrhosis and well developed gynecomastia, the urine was assayed for the follicle stimulating hormone. Each of the subjects excreted less than 5 rat units per 24 hours. Whether a smaller amount than normal was excreted is not known.

all had atrophic changes characteristic of absent ovarian function and had no evidence of estrogenic activity. All of these patients had decreased axillary hair. (Table III.) Only one of them had spider telangiectases and in this patient they were small and few.

One of the four oöphorectomized patients was found at autopsy to have changes in the breasts similar to those seen in gynecomastia in the male which were quite different from the simple atrophy usually seen in the castrated female. No explanation was found although the adrenals were carefully studied:

The one female patient with grade I cirrhosis was fifty-one years of age. Her men-

strual cycle had become irregular during the previous year. Pelvic examination showed that the genitalia were normal. The body hair was slightly decreased; the breasts were flabby but otherwise not remarkable.

One of two patients with cirrhosis of grade II severity was twenty-eight years of age. She still had cyclic menstrual bleeding and had no changes attributable to endocrine abnormality. The other individual was forty years of age. She had evidenced no definite change in libido. Definite facial and abdominal hirsutism had been present for three years but no virilization. There was no decrease in axillary hair. The menstrual periods were still cyclic but the duration and amount of bleeding had decreased. The breasts were small. Steroid excretion studies were not made in this patient so that the possibility that she might have had adrenal hyperplasia was not determined.

Of nine patients with cirrhosis of grade III severity, one was seventy-eight years of age and as far as could be ascertained had a normal climacteric some thirty years previously. She showed senile atrophy of the breasts and genitalia with complete loss of axillary hair. Although this patient had obviously had little or no ovarian function for many years, she had numerous small spider telangiectases.

Of the remaining eight women with grade III cirrhosis, seven had menstrual irregularities of various types. Two patients, forty-four and forty-five years of age, had amenorrhea for four months and one year respectively. The second of these patients had had menometrorrhagia for approximately one year before her menopause. A third patient, aged thirty-eight, had amenorrhea for eight months when first examined. At this time endometrial biopsy showed an extremely atrophic endometrium. Following adequate therapy with good compensation of liver function, this patient again began to have cyclic menstrual periods. Unfortunately, it was not possible to get another endometrial biopsy. One other patient with severe cirrhosis had infrequent bleeding with a normal amount of bleeding at each period.

The three remaining patients with menstrual changes had excessive bleeding. One of these patients required dilatation and curettage of the uterus. The endometrium was extremely hyperplastic.

These patients had other endocrine alterations associated with their menstrual changes. Five of the eight had decreased axillary hair; five had atrophy of the breasts. A sixth patient who had menometrorrhagia, uterine enlargement and a hyperplastic endometrium had numerous large nodules in both breasts. A clinical diagnosis of chronic cystic mastitis was made but no biopsy could be obtained. Six of these eight patients had spider telangiectases.

AUTOPSY FINDINGS

Adrenals. In eighty-seven patients with alcoholic cirrhosis no striking macroscopic changes in the adrenals were observed aside from tuberculosis in three subjects and hemorrhage in two women. Some of the glands were smaller and a few were larger than normal. On microscopic examination small cortical adenomas were found in two patients, focal fibrosis in two, marked vascular congestion in four and atrophy in one. There was lumen formation in seven individuals. In fourteen women there was infiltration of the cortices with varying numbers of lymphocytes and macrophages. A distinct decrease in lipid material was observed in most of the glands.

Pancreas. In twenty-eight of sixty-four patients examined there was fibrosis of the acinar portion of the pancreas, scarring being marked in some cases. In three instances there was hyalinization and scarring of the islets. In six subjects there were varying degrees of acute pancreatitis.

Testes. The data available do not permit an accurate evaluation of testicular lesions because microscopic sections were not taken in all cases. However, sections were made in twenty-three of fifty-six patients. There was definite atrophy of the germinal epithelium in eight with essentially no evidence of spermatogenesis. A primary carcinoma of the testis was present in one patient.

Prostate. Sections were made in twelve of the above subjects. These revealed benign prostatic hypertrophy in five patients, atrophy in one, carcinoma in one and metaplasia in one.

COMMENTS

Although much more study is needed to elucidate completely the rôle of the liver in the metabolism of steroid hormones, all available data indicate that it is an important one. It is to be expected that alterations in hormone physiology should occur in association with severe liver decompensation. This study of fifty-five male and sixteen female patients with cirrhosis of the liver has demonstrated the comparative frequency of endocrine changes among patients with this disease. The changes resulting from altered hormonal function which we observed consisted of the following: decrease in body hair, particularly of axillary hair; atrophy of the testes; decrease of libido and potency; sterility; menstrual disturbances; gynecomastia; telangiectasia and "liver" palms; decreased urinary excretion of androgens and 17-ketosteroids. Others have reported increased excretion of estrogen.²⁹

In males the earliest change usually is a decrease in libido, followed soon thereafter by a decrease in potency. Decreased sexual drive is apparently related to gonadal insufficiency which is demonstrable by clinical and pathologic examination. However, it is not yet known whether the decrease in testicular function is the result of depression of the gonad by the high level of circulatory estrogen which these patients develop as a result of decreased liver function, or to a suppression of pituitary gonadotrophic hormones. Although the majority of our patients had decreased sexual drive, a considerable number had never had normal libido. This lack of heterosexual drive may well be related to the fundamental physiologic conflict which led to chronic alcoholism.

Both male and female patients were often found to have decreased axillary hair which was probably due to a lessening of adrenal

activity. Other evidence also indirectly suggests decreased adrenal function. The 17-ketosteroid excretion of male patients with cirrhosis is lower than is usually found when gonadal steroid excretion alone is absent which suggests that adrenal hormone production, as well as testicular hormone formation, is less than normal. Necropsy examination of the adrenal gland shows a very low content of lipoid material. A few quantitative estimations of the cholesterol content of the adrenals have shown lower levels than are usually found in the adrenals of patients dying of chronic illnesses.¹⁰⁰ Electrolyte changes in patients with hepatic cirrhosis are not characteristic and alterations in carbohydrate metabolism, which might be attributed to adrenal insufficiency, are usually masked by the effects of the diseased liver. The relative lymphocytosis so frequently seen in patients with cirrhosis might possibly be the result of decreased adrenal steroid secretion. Some of the patients with liver disease who are pigmented and present a picture of "pseudo-Addison's disease" may actually have relative adrenal insufficiency.

Tepperman¹⁰² has suggested that since the cholesterol content of the adrenal gland, which might possibly be the precursor of the cortical steroid hormones, is largely in esterified form, inability of the diseased liver to esterify cholesterol may lead to a decrease in the manufacture of adrenal hormones. Another possibility is that the high level of estrogen in the blood may depress adrenal function. This effect has been demonstrated by Hamblen, Pattee and Cuyler,¹⁰³ who found that estrogen administration was followed by a decrease in urinary 17-ketosteroid excretion, presumably due to adrenal inhibition.

Part of the estrogen in each sex is probably secreted by the adrenal gland. Although it is likely that the total amount of estrogen formed is less than in the normal individual, ability of the liver to inactivate estrogen is so much impaired that the total circulating estrogen, particularly the unconjugated or biologically active form, is increased. The

increase in free estrogen could be considered as the cause of gynecomastia, metaplasia of the prostate and testicular atrophy. In the female, breast nodules and alterations in menstrual pattern probably result from increased level of estrogen. It is possible that

of many others who have found adrenal enlargement following estrogen administration or castration of male animals. It is probable that the same mechanism is at work in the production of adrenal stimulation in all of these situations. Probably

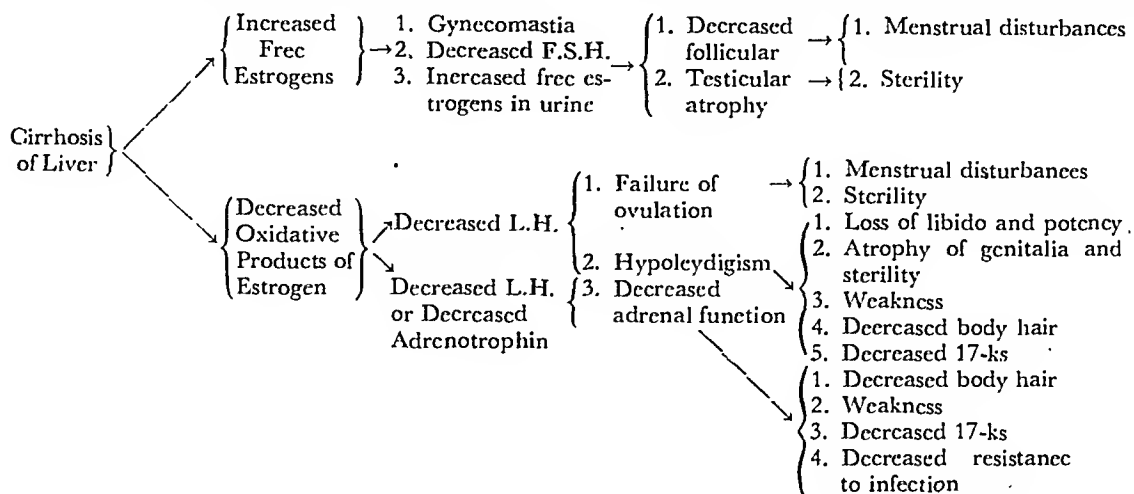


Fig. 3. A tentative hypothesis to explain endocrine changes associated with cirrhosis of the liver.

development of telangiectases in both sexes may be related to the high estrogen level.

The urinary gonadotrophin excretion was not elevated in three of our male patients. Smith and Smith¹⁰⁴⁻¹⁰⁶ have reported that release of luteinizing hormone from the pituitary gland occurs following administration of diethylstilbestrol or of such oxidative products of estrogen as Westerfeld's¹⁰⁷ lactone of estrone. If this mechanism of release of luteinizing hormone obtains in the human, it might be expected that luteinizing hormone would be released from the pituitaries of patients with cirrhosis of the liver who have high circulating estrogens. However, it may be that this does not occur because the estrogen is in a free and unoxidized form since Smith and Smith have reported that it is the metabolic products of estrogen and not the estrogen *per se* which causes release of luteinizing hormone from the pituitary gland.

A tentative hypothesis to explain adrenal insufficiency in these patients could be based on the observations of Smith and Smith that the lactone of estrone causes adrenal enlargement, of Levin¹⁰⁸ that diethylstilbestrol causes a decrease in adrenal cholesterol and

adrenotrophic hormone is released by the same stimulus that causes release of luteinizing hormone although the possibility must be considered that luteinizing hormone can stimulate the adrenal. This stimulation to the release of luteinizing hormone and of adrenotrophin is furnished by estrogenically inactive metabolic products of estrogen which are the result of one of the functions of the normal liver. The diseased liver is unable to inactivate estrogens and form these oxidative products.

The data accumulated suggest, as illustrated in Figure 3, that the liver may participate in steroid metabolism in the following manner: (1) It aids in the interconversion of estradiol and estrone and their conversion to estriol; (2) it participates in the formation of inactive oxidative products from estrogen; and (3) it conjugates estrogens for inactivation and excretion. With a marked decrease in these functions of the liver, the following sequence of changes might be expected to take place: free estrogen will accumulate in the blood and urine; associated with this there occurs a diminution in the release of follicle stimulating hormone, a suppression of spermatogenesis and follicle maturation

as well as estrogenic stimulation of target organs. The decrease in the inactive oxidative products of estrogen leads to a decreased release from the pituitary of luteinizing hormone and possibly of adrenotrophin. This, in turn, will result in menstrual abnormalities, decreased activity of the cells of Leydig and decreased adrenal function with loss of axillary hair and diminished urinary 17-ketosteroid excretion.

The foregoing explanations seem reasonable on the basis of available data. However, much more information is necessary to establish them as facts.

SUMMARY

A study has been made of endocrine functions in seventy-one patients with cirrhosis of the liver. These patients were graded I, II, and III according to the severity of their liver disease.

Fifty-five of the subjects were males and sixteen were females. Clinical endocrine changes observed in the male subjects consisted of decreased libido and potency, atrophy of the testicles, decreased body hair and gynecomastia. Telangiectasia and "liver palms" were also regarded as possibly being related to altered endocrine function.

Decrease in libido and potentia were found in thirty-seven of fifty-two (71 per cent) of the male subjects who could be questioned satisfactorily.

Decreased axillary hair was present in forty-six of the fifty-five male patients (84 per cent). Forty of the forty-six individuals with severe cirrhosis (87 per cent) had a decrease in axillary hair. The greatest decrease of body hair was found in this group.

Testicular atrophy was present in thirty-six of fifty patients (70 per cent) in whom the size of the testes was measured. Seventy-five per cent of the severe cases had atrophy of the testicles.

Gynecomastia was present in twenty-three of fifty-five patients (42 per cent).

Following injection of testosterone propionate intramuscularly, four male subjects had no increase in the quantity of 17-ketosteroid substances in the urine but two had

significant increase in the total excretion of androgens.

In three male patients in whom the urinary gonadotrophin excretion was assayed no increased excretion was formed.

In the females there were alterations in menstrual pattern, sexual drive, body hair, the uterus and in other target organs of estrogen including the breast.

Seven of eight female subjects who were in the reproductive age had menstrual abnormalities. Four of these patients had amenorrhea or infrequent bleeding. There was a decrease of axillary hair, atrophy of the breasts in five of these seven patients and chronic cystic mastitis in one.

In almost all of eighty-seven patients with Laennec's cirrhosis with postmortem examinations at the Mallory Institute of Pathology there was a decrease in lipid content of the adrenals and in eight of twenty-three patients there was atrophy of the testes.

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Complications of Alkalosis*

WILLIAM J. GRACE, M.D. and DAVID P. BARR, M.D.

New York, New York

IN 1945, we saw in consultation a patient who, during the course of treatment for intestinal obstruction, developed acute delirium with marked impairment of renal function. Further investigation revealed typical features of severe alkalosis. Prompt therapy with ammonium chloride was followed within a few hours by a dramatic change in the mental state and a slow but complete recovery of normal function of the kidneys. On reviewing the situation it was apparent that alkalosis had been precipitated by a combination of two factors: (1) frequent gastric lavage and (2) the administration of large amounts of sodium lactate in conjunction with the use of sulfadiazine.¹

During the course of the next few months we had occasion to see additional similar patients with alkalosis. Of the nine patients, six exhibited both delirium and renal insufficiency, two showed delirium only and one developed renal insufficiency without mental disturbance.

CASE REPORTS

CASE 1. C. S., a thirty year old white man, had a subtotal resection of his pancreas for hypoglycemia. Following the operation he was given daily intravenous injections of sodium lactate and sulfadiazine. Because of vomiting, gastric suction was started on the fifth postoperative day. He did not do well and continued to complain of nausea, vomiting, abdominal pain and headache. By the seventh postoperative day he was in a condition of semistupor. He was apathetic, lethargic, disorientated in time and place, respirations were slow and shallow and he became cyanotic. His extremities

were rigid but although muscle twitching was constant the Chvostek and Trousseau signs were negative. The following day he became semicomatose and only occasionally responsive. Cyanosis increased. The carbon dioxide combining power was 106 volumes per cent, the plasma chlorides were 310 mg. and the blood urea nitrogen was 74 mg. At this time he was given 20 Gm. of ammonium chloride intravenously. Four hours later he was mentally clear and alert. He ultimately recovered completely but the blood urea nitrogen did not return to normal until the twenty-first postoperative day. The urine remained normal throughout.

CASE 11. J. C., a fifty-seven year old white woman, was admitted to the Hospital because of a two day history of intestinal obstruction. An emergency exploration disclosed a loop of ileum obstructed by an adhesive band. The urine and the blood urea nitrogen were normal at that time. Following operation she was started on continuous gastric suction and was given injections of $\frac{1}{6}$ molar sodium lactate solution daily. During the first five postoperative days she gradually became more and more confused with increasing disorientation as to time, place and space. She became uncooperative, fought violently with her nurse, attempted to climb out of bed and pull out the nasal and intravenous tubes. During the sixth, seventh and eighth postoperative days she was restless, excited, disoriented and incoherent. The respirations became slow and shallow and cyanosis appeared. By the eighth hospital day her condition was critical. She was prostrate, delirious and stuporous. During the height of the delirium the urine contained +++ albumin and hyaline and granular casts. The carbon dioxide combining power was reported as "over 90." The value of chlorides in the plasma was 420 mg.

* From The Department of Medicine, New York Hospital and Cornell University Medical College, New York, N. Y.

TABLE I
CLINICAL DATA BEFORE AND AFTER TREATMENT
OF ALKALOSIS

Patient	Date	Blood Serum Levels		
		CO ₂ , Vols. %	Blood Urea Nitrogen, Mg. %	Chlorides, Mg. %
C. S.	8/31	63		540
	9/6	106	74	310
	9/7	106	50	350
	9/7	Ammonium chloride started		
	9/17	62	21	510
J. C.	12/24	78	18	480
	12/26	90+	29	445
	12/27	90+	63	
	12/30	Ammonium chloride started		
	12/30	75	35	430
J. L.	1/11	74	13	610
	11/15	64	40	
	11/26	110	73	
	11/29	104	66	520
	11/29	Ammonium chloride started		
P. M.	12/2	87	42	500
	12/6	69	39	
	1/16		59	
	1/17	81	71	380
	1/18	76	75	420
A. R.	1/20	Ammonium chloride started		
	1/24	61	31	620
	7/3		15	
	7/16 (a.m.)	90+		349
	7/16	Gastric suction and sodium lactate discontinued		
C. G.	7/16 (p.m.)	70	33	
	6/19	100+	16	
	6/20	100+		334
	6/21	Ammonium chloride started		
	6/21	80+		378
W. P.	6/25	63	8	525
	4/15	90+		347
	4/19	90+		246
	4/19	Treatment started		
	4/20	68		485
H. H.	5/8		25	580
	5/10	Gastric aspiration discontinued		
	5/22		44	
	5/23	Alkali discontinued		
	5/25	81	61	
D. O.	6/4		33	
	10/26		24	
	2/18		22	
	3/30	90	32	
	3/31	Ammonium chloride started orally		
	4/2	66	36	578
	4/4	60	29	
	4/22	Gastroenterostomy		
	4/25	80	20	535

and the blood urea nitrogen was 63 mg. On the eighth postoperative day, gastric suction and sodium lactate were discontinued and she was given 20 Gm. of ammonium chloride intravenously. Within a few hours after the infusion there was a dramatic clearing of the sensorium and she became orientated and cooperative. Her respirations attained normal depth and frequency and the cyanosis disappeared. The remainder of the hospital course was complicated by pulmonary emboli but she eventually made a complete recovery. The urine became normal after the twelfth postoperative day, although the blood urea nitrogen remained elevated until the twenty-sixth hospital day.

CASE III. J. L., a fifty-five year old white man, was admitted to the Hospital because of unexplained intestinal obstruction. He was started on gastric suction. During the hospital course he developed mild bronchopneumonia for which he was given parenteral sulfadiazine and sodium lactate. He recovered promptly from the pneumonia but as the pneumonitis subsided he became delirious, disorientated in time and place, had visual hallucinations and was incontinent of bladder and bowel. He was facetious, assaultive and uncooperative. He repeatedly attempted to climb out of bed, pulled out infusion tubes, struck a nurse and attempted to strike a physician and a consulting psychiatrist. At the height of this mental disturbance the carbon dioxide combining power was 110 volumes per cent and the blood urea nitrogen was 73 mg. The urine showed ++ to +++ albuminuria (but no formed elements) for six days. Because of the aberrations in the blood chemical findings, the gastric suction was stopped as was the sodium lactate and he was given 4 Gm of ammonium chloride daily by mouth for five days. During the next few days the mental state cleared and he became oriented, alert and cooperative. The CO₂ combining power was normal on the fourth day. Although he subsequently died of carcinomatosis there were no other episodes of disorientation and the carbon dioxide combining power remained within normal limits.

CASE IV. P. M. was an emphysematous sixty year old white man whose renal function on a previous admission had been found to be nor-

mal. For a year he had been on a Sippy diet and had taken alkaline powders. For five months he had vomited with increasing frequency and three days before admission he vomited a large amount of bright red blood. At the time of entry to the Hospital he was found to be completely disorientated in time and place. He was drowsy, apathetic and had paranoid delusions. There was constant muscular twitching of the extremities although the Chvostek and Trousseau signs were absent. The remainder of the examination was normal. Blood pressure was 120/68 and there were no signs of vascular disease. The urine showed + albuminuria for a few days only. During the first seven hospital days he was kept on a Sippy regimen and given alkaline powders. On this program the disorientation increased and he became more apathetic and drowsy. Finally he became completely uncooperative and was incontinent of urine and feces. Muscular twitching was constantly present. At the height of this mental disturbance the carbon dioxide combining power was reported as "over 80," blood chlorides were 380 mg and the urea nitrogen was 71 mg. Treatment was then changed and he was started on venoclysis of sodium chloride and was given ammonium chloride by mouth. Within twenty-four hours the patient was completely oriented and his paranoid delusions had disappeared. The rest of his sojourn in the hospital was uneventful. An x-ray of the gastrointestinal tract revealed a duodenal ulcer without obstruction and he was discharged with complete control of his gastric symptoms. Ten months later renal function tests still showed impairment of kidney function.

CASE V. A. R., a sixty-six year old physician, was admitted to the Hospital for resection of a malignant lesion of the ascending colon. Postoperatively she was started on gastric suction and given sulfadiazine and sodium lactate daily. On the fifth postoperative day she was found to be disorientated in time and place and was talking incessantly to herself. On the sixth postoperative day she was still cloudy mentally and on this day she had a severe, generalized epileptiform seizure of several minutes' duration. The following day she was found trying to climb out of bed, was very uncooperative, talked incoherently and was disorientated and irrational.

She did not recognize any of her relatives, nurses or physicians and was incontinent of urine and feces. During the height of this mental disturbance the carbon dioxide combining power was reported as "over 90" and blood chlorides as 349 mg. The ECG showed a long Q-T interval. Because of these findings the sodium lactate and gastric suction were discontinued. The following day the patient was found to be mentally clear, alert, oriented and cooperative and the carbon dioxide combining power was 70 volumes per cent. The blood urea nitrogen did not rise above 33 mg. and the urine remained normal throughout.

CASE VI. C. G., a forty-five year old white man, was admitted to the Hospital because of a four-day history suggestive of intestinal obstruction. At exploration a pelvic abscess was found and drained but no obstructive lesion was discovered. Postoperatively he was started on gastric suction and was given sulfadiazine, sodium lactate and penicillin. The patient did well for a few days postoperatively when he became disorientated, uncooperative and violently belligerent. He fought with his attendants, repeatedly climbed out of bed, broke restraints and attempted to pull out the gastric suction and infusion tubes. During two days of this behavior the carbon dioxide combining power was reported as "over 100" and his blood chloride fell to 334 mg. Chvostek and Trousseau signs were positive and the blood calcium fell to 8.1 mg. An electrocardiogram showed typical features of hypocalcemia. He was given 40 Gm. of ammonium chloride parenterally during the day and night, and on the following day there was complete clearing of the disorientation and the patient became mild and cooperative. It is noteworthy that throughout his alkalosis the blood urea nitrogen did not rise above normal and the urine was normal during the episode.

CASE VII. E. P., a fifty-three year old markedly emphysematous man, was admitted to the Hospital for a perforated peptic ulcer. Postoperatively he was placed on gastric suction, given intravenous sulfadiazine and sodium lactate and at first did well. On the ninth postoperative day, however, he was slightly disorientated and did not recognize his relatives. On

the following day he was found in a state of confusion with a pronounced word aphasia. Three hours later he became semiconscious, would not respond to his name and resisted examination. The respirations were slow and shallow and he was cyanotic. There were numerous muscular twitchings and the extremities were spastic. At this time the carbon dioxide combining power was reported as "over 90" and the blood chlorides were 246 mg. (42 mEq.). He was given 20 Gm. of ammonium chloride by gavage in 1,000 cc. of water. At the end of this time his mental state had improved so that he was able to identify himself, name objects and respond to commands. The carbon dioxide was again reported as over 90 volumes per cent and he was given another 20 Gm. of ammonium chloride by gavage. At the completion of this treatment the carbon dioxide combining power was reported as 59 volumes per cent, the chlorides were 485 mg. and the patient was well orientated and cooperative. The blood urea nitrogen remained normal throughout.

CASE VIII. H. H., a fifty-six year old white man, was admitted to the Hospital for symptomatic treatment of intractable pain from a peptic ulcer. The general physical examination was essentially negative except for emphysema. He was given a diet of milk, cream and alkali powders. On this regimen he did well and the pain gradually abated. On the twelfth hospital day, however, he began to complain of headache, drowsiness and generalized weakness. He was noted to be apathetic and, although previously active, chose to remain in bed all day. During the next few days the drowsiness continued; he was disgusted with his milk feedings. He became restless, vomited more frequently and exhibited muscular twitching. The urine, which was normal on admission, for twelve days during the period of alkalosis showed albumin, microscopic hematuria and hyaline and granular casts. After this period it was normal.

CASE IX. D. O., a seventeen year old white boy, was admitted to the Hospital because of vomiting from peptic ulcer. During the height of one of the obstructive periods the carbon dioxide combining power rose to "over 90" and the blood urea nitrogen to 36 mg. Carpopedal spasm was noted during this episode. Following

gastroenterostomy his blood chemical findings returned to normal. Throughout all of the hospital course, however, there was never any disturbance of the sensorium and the urine remained normal throughout. Unfortunately, there has been no determination of renal function since his discharge from the hospital.

COMMENTS

Eight of the nine patients were seen in consultation on the surgical service. Primary conditions included one subtotal pancreatectomy designed to correct hypoglycemia, two patients with intestinal obstruction, one patient with pelvic abscess simulating intestinal obstruction, one with cancer of the colon without obstruction and four patients with peptic ulcers. Three of the patients with peptic ulcer were also emphysematous. The cause of the alkalosis could be attributed in six of the nine patients to the simultaneous use of gastric lavage and the liberal use of sodium lactate with or without sulfadiazine. In two of the emphysematous patients with peptic ulcer, the administration of Sippy powders or similar alkaline treatment seemed to be the exciting cause. In one patient without emphysema, alkalosis appeared to be attributable to continued vomiting.

Both mental disturbance and renal insufficiency were apparent in six of the nine patients. Two showed delirium only, and one developed renal insufficiency without mental disturbance. During the alkalosis respiration became shallow and slow and in some instances so inefficient as to result in cyanosis. Muscular twitching and spasticity were observed in one patient. In another, there were carpopedal spasms, while in still another patient there was a severe generalized epileptiform seizure of several minutes' duration. It was notable, however, that in only one patient could the Chvostek or Trousseau signs be elicited. The highest recorded carbon dioxide combining power was 110 volumes per cent, although in a

number of patients the value was reported approximately as "over 90" or "over 100" volumes per cent. Definite lowering of chloride values accompanied the increases in bicarbonate. In one instance the very low value of 246 mg. per cent was found. The urinary picture varied. In three patients no abnormalities were found during the episode of alkalosis. All of the other patients showed slight or moderate albuminuria. Hyaline and granular casts appeared frequently and in one patient microscopic hematuria was evident. Blood urea nitrogen was elevated and in three patients attained levels of over 70 mg. per cent.

Much more impressive than these signs, however, were the changes which took place in the sensorium. Usually the first abnormality to be noted was a slight change in the personality. Patients who were previously cooperative and placid became irritable, exaggerated their complaints, sought extra attention or were excessively demanding. One man who was on a regimen of alkaline powders for peptic ulcer lost his taste for milk and complained of nausea. Several suffered from a dull, aching headache of muscle spasm type. In one instance, it resembled vascular headache with throbbing pain of high intensity and hemicrania. Vomiting was observed and in one patient was frequent and violent. Generalized weakness was apparent but at times was accompanied by muscular twitching and hyperreflexia. Activity was lessened, mentality appeared to be dulled and drowsiness, apathy or lethargy developed. Accompanying these manifestations there was disorientation in time and place, often with belligerent uncooperativeness. Eight of our patients at one stage became completely disorientated with marked changes in personality. One struck a nurse and a doctor. Others tore out venoclysis needles or gastric suction tubes. Some tried to climb out of bed dragging infusion apparatus with them. When the state of alkalosis was allowed to

continue, evidence of profound derangement of function of the nervous system became manifest. One of our patients had a severe generalized convulsion, another developed anomia.

In presenting the record of these cases there can be no claim of discovery or originality. It has long been known that alkalosis may result either from the loss of large amounts of the acid secretion of the stomach, or from the ingestion of excess amounts of alkaline medication.^{2,3} Since 1915, when Sippy introduced the use of alkaline powders for the treatment of peptic ulcer, it has been realized that not all patients are able to tolerate them and that 5 to 10 per cent of them will develop considerable degrees of alkalosis.² As long ago as 1923, Hardt and Rivers³ in their excellent study of the basis of symptoms in alkalosis, reported that their patients were irritable and introspective, complained of headache, nausea, vomiting and weakness, that their respirations were slow and that they were prostrated and drowsy. They also found that the urine of such patients might, during alkalosis, show albumin, red blood cells and casts which would disappear with the return of the carbon dioxide combining power to normal levels. Later studies by many observers have revealed evidence of serious renal derangement or of actual nephritis developing during periods of alkalosis and persisting for variable intervals following cessation of the alkalotic state.³⁻⁹

There are, however, a number of circumstances connected with our observations that seem to deserve some emphasis. A great majority of previous studies have been concerned with alkalosis developing in patients with peptic ulcers who were treated with alkaline powders, and severe vomiting which accompanies gastric conditions and intestinal obstruction resulted. In six of our patients, on the other hand, symptoms appeared to develop as a result of a com-

bination of gastric suction and the administration of sodium lactate, both measures which at present have great vogue and a high measure of utility in post-operative conditions.

The danger of removal from the body of large amounts of acid secretion is not always kept in mind, nor is it always realized that the very useful sodium lactate solution may add greatly to the store of sodium bicarbonate unless corrected by the simultaneous administration of sodium chloride. It is worthy of note that at the time these patients were seen in consultation there was no realization of their true state on the part of those who had attended them. To them it was disturbing indeed to witness in the course of a previously satisfactory postoperative convalescence, the development of disgust for food, nausea, vomiting or irritability and disorientation with subsequent apathy, lethargy, stupor or spasticity, twitching and even convulsive seizures. When these symptoms were combined with increasingly abnormal urinary findings and an alarming retention of non-protein nitrogen, there was much cause for confusion in diagnosis unless one were aware of all the consequences of the alkalotic state.

Another aspect which deserves inquiry is the persistence of renal damage arising from the continuance of alkalosis. From our own observations and from many more in the literature there is reason to believe that recovery of normal renal function may be long delayed and that pathologic changes may persist even in patients who have previously exhibited no signs of kidney disease.^{5,8,9,10} One of our patients showed retention of non-protein nitrogen twelve months after the alkalotic episode. In the literature similar observations are numerous^{5,6,7,11} and in the case of Brown and Eusterman¹² impaired renal function was demonstrable even after six years. Such records lead to a disturbing fear that alkalosis may not be an entirely

temporary and trivial phenomenon and indicate that the prevention or prompt correction of the condition may be of considerable importance to the subsequent health of the individual.

Still another circumstance in our observations may deserve passing comment. In three of the four patients who developed alkalosis during the treatment of peptic ulcer with alkaline powders, there was a preexisting emphysema. It seems possible that the tendency to elevated bicarbonate which develops in emphysematous patients may render them more than ordinarily susceptible to the consequences of alkalosis when they are given alkaline therapy.^{13,14}

In the management of alkalosis it is important to realize that the situation will correct itself rather promptly if the cause can be removed. In several of our patients spontaneous remission occurred when the alkaline powders were withdrawn or the gastric suction and parenteral administration of lactate solution were discontinued. In others, however, it appeared necessary or very desirable to obtain prompt effects. To accomplish this ammonium chloride was given parenterally by the method of Zintel, Rhoads and Ravdin.¹⁵ Briefly, the method consists of the intravenous administration of autoclaved 2 per cent solution of ammonium chloride in distilled water. The usual procedure was to administer a liter of such a solution (20 Gm. ammonium chloride) over a period of two and one-half to three hours. The results were satisfactory and frequently dramatic, with almost immediate improvement in the orientation and cooperation of the patient as well as rapid disappearance of the disturbing symptoms.

SUMMARY AND CONCLUSIONS

1. The current use of gastric suction and sodium lactate solutions may lead to a condition of alkalosis which may be accompanied by changes in personality, delirium,

stupor or convulsions and by renal insufficiency which tends to persist.

2. The state is often unrecognized and if neglected may lead to serious consequences.

3. Removal of the causes of the alkalosis will lead to gradual or fairly prompt recovery of the abnormal mental state. A more rapid correction may be accomplished by the parenteral administration of ammonium chloride.

4. It is possible that emphysematous patients are more than ordinarily susceptible to alkaline therapy.

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Electrolyte Partition in Patients with Edema of Various Origins*

Sodium and Chloride

EDITH B. FARNSWORTH, M.D.

Chicago, Illinois

THE orthodox concept of edema as a physicochemical phenomenon involving the extravasation, primarily of saline solution, over the peripheral capillary barrier between blood stream and extracellular tissue fluid has been challenged in recent years by numerous observers. The postulated normal equilibrium between hydrostatic pressure outward and oncotic pressure inward has been a serviceable hypothesis since most medical entities have been associated with a disturbance of one or the other of these vectors. Thus, the teaching that "in cardiac decompensation stasis causing increased hydrostatic pressure in the capillary bed is apparently the important factor in causing edema"† has long been standard. Increased hydrostatic pressure in the capillary was plausible enough in view of the demonstrable increase in venous pressure characteristic of heart failure. Similarly, other disease processes, notably cirrhosis and nephrosis, in which fluid retention is present have been characterized by the reduction of some constituent of the blood, chiefly albumin, to which could be attributed a diminution of oncotic pressure and hence the production of edema.

Discrepancies in this system have been pointed out, both in heart failure and in the hypoproteinemic states, but the attention of research workers and clinicians alike

has remained, for the most part, directed toward events taking place at the capillary membrane. That the kidneys participate actively in the "retention of salt and water" was, however, at least strongly implied by Schroeder and Futeher in 1942.¹ These workers studied a group of five cardiac patients and two controls and found that doses of salt and water were imperfectly excreted by the experimental group as compared with the two normal subjects. They found, in addition, that the urea clearance capacity of the cardiacs was not diminished and that mercurial diuretics promoted the output of salt and water. Their studies brought out three questions: first, was the decreased excretion of salt and water due to decreased renal filtration rate; second, were circulatory changes demonstrable in the kidneys and third, was tubular behavior due to the influence of a hormone? This viewpoint was supported in 1944 by Warren and Stead² who formulated the events of edema formation in cardiac failure as prefaced by impaired cardiac function which by unknown mechanisms led to decreased renal excretion of sodium and water and, thereby, to increased blood volume and elevated venous pressure.

Our own experience³ with a massively decompensated patient upon whom repeated clearance determinations of inulin, diodrast, chloride, phosphate and sodium were performed, indicated that profound disturbances of renal physiology were reflected,

† Peters and Van Slyke. Williams & Wilkins, Baltimore, 1932.

* From the Department of Medicine, Northwestern University Medical School, Chicago, Ill. Funds were furnished by the U. S. Public Health Service, Research Division.

not in a reduction of working nephrons and hence diminution of filtration rate, but in an altered manner or pattern of tubular reabsorption of sodium and chloride. Thus, the acute fluid retention and oliguria of severe decompensation could not be correlated with a failure on the part of the glomeruli to filter but rather with a sharp increase in the tubular reabsorption of water and sodium and a variable behavior toward chloride. A recent paper of Reaser and Burch⁴ reports a retention of sodium in cardiac decompensation, demonstrated by the use of radioactive sodium, a finding which contributes to the concept that the conversion of fluid equilibrium into positive fluid balance is not accomplished without tubular intervention.

The validity of hypoproteinemia as a cause of hepatic cirrhosis, on the other hand, has also been questioned. Absence of agreement on the part of students working with inert membranes as to the critical concentration of albumin in the maintenance of fluid equilibrium has been striking and in 1945 Ralli and co-workers⁵ reported no correlation between plasma albumin and the presence of ascites. They went on to show that an antidiuretic hormone was present in augmented concentration in the urine of patients with ascites and postulated that the liver normally inactivates the antidiuretic hormone.

The present study was undertaken for the purpose of defining more specifically the renal aspects of water and electrolyte balance in congestive heart failure.

Methods. Sodium and chloride clearances were determined in a group of cardiacs who gave evidence of fluid retention. No attempt was made to classify the etiological factor.

The first group of controls consisted of normal individuals. The second group was intended to consist of patients suffering from edema of other than cardiac origin. The findings in the latter group, however, broke down into patterns which evidently represented characteristics of the two other types of edema studied, namely, hepatic

cirrhosis and the nephrotic syndrome. The problem was, therefore, reorganized as a study of the sodium-chloride ratio in (1) congestive heart failure, (2) hepatic cirrhosis and (3) nephrosis.

The data were found to be more significant when considered in terms of milliequivalents of urine sodium and chloride undiluted by the relatively unvarying plasma concentration; the study was continued on single morning urine specimens. Since conclusions based upon single specimens alone might be considered unreliable, several twenty-four-hour outputs have been added.

All cardiac patients with edema had been on low sodium diets for variable periods and all were taking ammonium chloride. Most cirrhosis patients were on normal salt intakes; a few received ammonium chloride as did several of the nephrosis cases. For the purpose of evaluating a diuretic management under the conditions of the present study four normal individuals were included before and after a period of three to fifteen days on a similar regimen.

Nine patients giving evidence of water retention as a result of various kinds of heart failure were studied by means of sodium and chloride clearances. The tests were performed in the morning in the fasting state. The patients were permitted to drink water as they chose. The control series consisted of thirteen subjects who were free of heart disease or of edema on any other basis. Two clearance periods of two hours each were determined, the blood specimen being drawn at the end of the first period and immediately centrifuged. The continuation studies included urine samples on twenty-two cardiacs, twenty-one normal subjects, eighteen patients with hepatic cirrhosis and eight with nephrosis.

The sodium ion concentration in urine and serum filtrate was determined nephelometrically after precipitation as sodium magnesium uranyl acetate, according to a modification of the method of Lindsay and his co-workers.⁶ The readings were made by means of a two-cell photoelectric nephelometer with a reproducible accuracy of

3 per cent. The chloride determinations were made by titration with mercuric ion, using s-diphenyl-carbazone as an indicator.⁷ This method was found to be comparable in accuracy to that of Whitehorn or Volhard.

Determinations on twenty-four-hour col-

TABLE I
CARDIAC DECOMPENSATION

Patient	Sodium Clearance	Chloride Clearance	Clearance Ratio	mEq./L. Sodium	mEq./L. Chloride	mEq. Ratio
1	0 07	0 65	0 10	9	82	0 11
2	0 18	1 38	0 15	5	49	0 10
3	0 10	0 24	0 44	31	56	0 55
4	0 27	1 1	0 24	36	107	0 30
5	0 64	1 5	0 42	116	180	0 64
6	0 21	0 43	0 49	67	100	0 67
7	0 52	1 4	0 37	30	69	0 50
8	0 02	0 17	0 11	2	15	0 13
9	0 06	0 13	0 48	17	31	0 55
10				42	77	0 55
11				3	10	0 30
12				28	85	0 33
13				75	110	0 68
14				73	155	0 47
15				10	15	0 67
16				11	31	0 35
17				66	125	0 53
18				4	13	0 31
19				33	86	0 38
20				1	10	0 10
21*				5	34	0 13
22*				2	52	0 04
Average				0 32		Average
						0 40

NORMAL

1	0 41	0 65	0 63	120	140	0 86
2	0 77	1 3	0 59	96	107	0 90
3	0 83	1 2	0 69	110	120	0 92
4	0 56	0 77	0 73	97	99	0 98
5	0 50	0 83	0 60	29	33	0 88
6	0 83	1 4	0 59	74	90	0 82
7	0 66	1 1	0 60	150	180	0 83
8	0 96	1 7	0 56	140	180	0 78
9	0 87	1 3	0 67	210	230	0 91
10	0 88	1 3	0 68	160	170	0 94
11	0 84	1 5	0 56	140	180	0 78
12	0 93	1 3	0 72	100	100	1 00
13	0 76	1 2	0 63	130	140	0 93
14				198	197	1 00
15				100	170	0 94
16				230	260	0 89
17				140	135	1 04
18				130	140	0 93
19				140	170	0 82
20				180	200	0 90
21*				37	46	0 81
Average				0 63		Average
						0 90

* Twenty-four-hour specimens quoted in milliequivalents per twenty-four hours.

lections employed the standard method of Volhard for chloride and colorimetric readings of the uranyl acetate precipitate for sodium.

Results. Table 1 shows the clearance studies. The average ratio of sodium to chloride clearance in the cardiac group was found to be 0.32, with a range of 0.10 to 0.49. The control subjects gave an average ratio of 0.63, with a range of 0.56 to 0.73.

TABLE II

Normal Regimen					Low Salt, Acid Ash Diet, Ammonium chloride 4 Gm. Daily		
Patient	mEq./L. Sodium	mEq./L. Chloride	Sodium Chloride	Days	mEq./L. Sodium	mEq./L. Chloride	Sodium Chloride
1	106	106	1.00	4	58	80	0.72
2	146	202	0.73	3	81	86	0.94
3	113	113	1.00	8	61	67	0.91
4	45	48	0.94	14	43	43	1.00
			Average				Average
			0.92				0.89
Cirrhosis				Nephrosis			
1	*	79			26	31	0.84
2	*	43			19	26	0.73
3	*	32			65	72	0.90
4	14	41	0.34		70	67	1.04
5	23	80	0.29		82	77	1.07
6	*	63			73	85	0.86
7	*	39			80	72	1.11
8	9	60	0 15		65	79	0.82
9	19	80	0.24				
10	52	110	0.47				
11	59	132	0.45				
12	9	55	0.16				
13	2	60	0 03				
14	19	75	0.25				
15	2	15	0.13				
16	4	31	0.13				
17	5	86	0.06				
18	45	77	0.58				
19	30	133	0.23				
			Average				Average
			0.25				0.92

* Below 2.

The continuation studies are presented in Tables 1 and 11. The cardiac patients showed a sodium-chloride ratio, in milliequivalents, of 0.10 to 0.67, with an average of 0.40 compared with a control average of 0.90. Four normal subjects averaged 0.92 without salt restriction and 0.89 after a period of salt restriction and medication of ammonium chloride, 4 Gm. daily.

Sodium was markedly reduced in the cirrhosis group. Chloride excretion was also depressed but the average sodium-chloride ratio was considerably below that found in the cardiac group.

The nephrotic syndrome, on the other hand, showed a normal sodium-chloride partition.

COMMENTS

Assuming that sodium is as freely filterable in the extrarenal pathological states under discussion as in the normal conditions upon which present concepts of renal dynamics were established, the tubules are seen in these studies to exercise definite selectivity in the reabsorption of certain electrolytes. Whatever may be the exchange at the capillary membrane, the activity of the renal tubules is clear. We are dealing then with conditions in the kidneys which are mediated by the blood stream and are somehow correlated with an increase in the volume of extracellular tissue fluid and hence an increase in the total body sodium. It is evident that the augmented extracellular fluid compartment could only affect the kidneys by means of the blood stream but, since the blood concentrations of electrolytes are known to be normal, such a mechanism would be difficult to conceive. If, on the other hand, some other factor capable of modifying tubular reabsorption of sodium and chloride could be stimulated by changes in the composition of extracellular tissue fluid, those changes would be likely to include alterations in the sodium or chloride concentrations. The composition of ascitic and edema fluid have been found, however, to show no such alterations; so although it is possible that some other change in the extracellular tissue fluid could initiate a process which could in turn act on the renal tubules, it seems rather more probable that the altered reabsorptive faculties of the tubules precedes the extravasation phenomenon at the capillary membrane. The results shown here, as well as the conjectures which they stimulate, are compatible with the postulates of Warren and Stead.²

Considering now the ease of cirrhosis with fluid retention, the almost total absence of sodium in the urine is difficult to reconcile with the orthodox view of fluid storage on

the basis of hypoproteincemia, portal obstruction or increased intra-abdominal pressure. The present study shows a relative and an absolute decrease in sodium excretion but, since the data do not include a time element, the retention of water and the increased excretion of chloride characteristic of the pitressin action suggested by the New York group⁵ cannot be demonstrated. It is clear, however, that the renal tubules are playing a rôle which earlier theories failed to consider and it is probable that they are responding to a factor which may be primarily hormonal or chemical.

In contrast with the electrolyte pattern of hepatic cirrhosis and of cardiac decompensation, the nephrotic syndrome showed no deviation from normal in the sodium-chloride ratio. This finding is striking, since cirrhosis and nephrosis have the common factor of hypoproteinemia and might, therefore, have been expected to show a similar urine electrolyte pattern.

CONCLUSIONS

The formation of edema in cardiac decompensation and in hepatic cirrhosis is associated with a decrease in the ratio of urine sodium to chloride in terms of milliequivalents.

The edema of nephrosis cannot be identified with any alteration in the urine sodium-chloride ratio. The demonstration of specific and characteristic electrolyte patterns in edema of various origins suggests that the kidney plays an active rôle in the establishment and maintenance of certain types of fluid retention.

SUMMARY

Data have been collected on electrolyte partitions in urine of patients with (1) congestive heart failure, (2) hepatic cirrhosis and (3) nephrosis, for the purpose of demonstrating renal function in fluid retention associated with these entities.

Clearance evaluation of sodium and chloride in cardiac decompensation and in normal subjects showed a decrease in sodium clearance with respect to chloride

in the cardiac group. Comparison of sodium to chloride in milliequivalent ratios showed a constant decrease in sodium excretion and a depression in the sodium-chloride ratio. This depression varied directly with the severity of the disease process and the degree of fluid retention. These findings are compatible with the hypothesis that edema is a result of retention of sodium by the renal tubules rather than of increased venous pressure.

Patients with hepatic cirrhosis were found to release greatly reduced amounts of sodium; several showed only traces. In this group, the sodium-chloride ratio was even more sharply reduced than in the cardiac group. Such evidence of pathological physiology in the kidney is difficult to reconcile with the widely held theory that fluid retention in cirrhosis is inversely proportional to the plasma albumin concentration.

No disturbance in the normal sodium-chloride ratio could be found in nine patients with nephrosis.

It was concluded that fluid retention in cardiac decompensation and in hepatic cirrhosis is not due solely to increased hydrostatic and decreased oncotic pressure, respectively, but to disturbances of electrolyte metabolism intimately associated with the renal tubules.

I wish to acknowledge with gratitude the generous help of the attending and resident staff of Passavant Memorial Hospital, Dr. Janet

Kinney and the resident staff of the Cook County Hospital and Dr. H. H. Boyle and his service at Children's Memorial Hospital. Without such cooperation, the collection of clinical material would have been extremely difficult.

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Serum Concentrations of Penicillin G in Man Following Intramuscular Injection in Aqueous Solution and in Peanut Oil-Beeswax Suspension*

HAROLD A. TUCKER, M.D. and HARRY EAGLE, M.D.
Baltimore, Maryland

THE therapeutic action of penicillin probably rests to a large extent on its direct bactericidal action. In order to kill the largest number of organisms in the shortest possible time it is therefore necessary to provide at the focus of infection a concentration which is maximally effective for the particular organism. This tissue concentration of penicillin is obviously not susceptible of direct measurement. The serum concentration of penicillin can, however, be determined; and although such factors as the binding of penicillin by serum proteins,¹ its varying rate of diffusion out of the blood into the several tissues and its binding or destruction in the tissues,^{2,3} enjoin caution in the interpretation of the blood level data, these do provide information as to the concentration of penicillin available for distribution at any one moment.

It is therefore of some therapeutic interest to know the average serum concentration provided by a given dose of penicillin at varying periods after its administration. With that information, one can estimate how often a given dose of penicillin should be repeated in order to maintain at the focus of infection a concentration effectively bactericidal for the particular organism. The available data with respect to the

serum concentrations of penicillin in man⁴⁻⁹ deal largely with amorphous preparations containing several penicillin species in unknown proportions.¹⁰ The data herein reported are based entirely on preparations of crystalline sodium penicillin G.

MATERIALS AND METHODS

One hundred thirty-eight patients from the Johns Hopkins Hospital were used in this study; 110 were in-patients and 28 were undergoing ambulatory treatment for gonorrheal infections. Eighty-three were males. The study was limited to patients who had received no penicillin during the forty-eight hours preceding the test and whose renal and cardiac functions were essentially normal. No limitations were placed on fluid intake or on the degree of physical activity.

For injection in aqueous solution two lots of crystalline penicillin G from two different manufacturers were employed. One was a commercial lot and the other was a highly purified sample prepared for experimental use. The results with the two lots did not differ demonstrably and they are not distinguished in the tables. For administration a 6 per cent solution (60 mg. per cc., equivalent to 100,000 Oxford units) was prepared. The volume injected was then adjusted to the body weight to give

* From the Syphilis Section of the Medical Clinic of the Johns Hopkins Hospital and the Laboratory of Experimental Therapeutics of the U. S. Public Health Service and the Johns Hopkins School of Hygiene, Baltimore 5, Md. A part of this work was supported by a grant from the Research Grants Division, National Institute of Health, U. S. Public Health Service.

dosages of 10, 3, 1.5, 0.6, 0.3, or 0.15 mg./Kg. (total dosages of 1,200,000 units down to 18,000 units in a man weighing 72 Kg. or approximately 160 pounds). The largest single injection was 12.0 cc. (1,200,000 units) and the smallest was 0.11 cc. (11,000 units). The outer upper quadrant of the buttock was the site of injection; the plunger was withdrawn prior to injection in order to avoid intravenous administration. All tests were begun at approximately 9 A.M. and blood samples were taken by venipuncture at appropriate intervals.

Four lots of crystalline penicillin G suspended in peanut oil and beeswax from two different manufacturers were used in the experiments with that preparation. All contained 180 mg. (300,000 units) per cc. Following preliminary warming in a water bath at 40 to 50°C., the material was withdrawn into an unheated, dry-sterilized syringe of appropriate capacity. In making the injection, a dry 20-gauge needle was first inserted into the gluteal muscles. If no blood appeared within a few seconds, the syringe containing the suspension was attached and the operation completed. Tests were begun at either 9 A.M. or 9 P.M. No embolies or allergic phenomena were noted and the transitory, local discomfort was readily explained on the basis of the volume of material injected. The largest dose employed was 4.0 cc., equivalent to 1,200,000 units and the smallest was 0.35 cc. (105,000 units).

The sera were assayed by a modified Kirby-Rantz method involving the use of serial dilutions of serum, and in which inhibition of hemolysis by the C-203 strain of *Streptococcus pyogenes* was the end point.¹¹ All the assays were corrected for the inhibitory effect of human serum on penicillin activity *in vitro*,^{1,11-13} using the corrective factors determined by one of us for this particular assay method.¹⁴ The serum concentrations are expressed in the figures and tables as both micrograms and units of penicillin G per cc. of serum, 1 microgram being equivalent to 1.67 Oxford units.

BLOOD LEVELS AFFORDED BY PENICILLIN G IN AQUEOUS SOLUTION

In Table 1 are shown the median serum concentrations observed one-half, one, two, four and eight hours after the injection of penicillin G in aqueous solution. The data are presented graphically. (Fig. 1.) Every value in either Table 1 or Figure 1 is based on a minimum of ten subjects injected at each dosage level and tested at each time period. Table 1A gives the range of variation in the individual subjects, the standard deviation from the median and the standard error of the median for each dosage level and at each time period tested.

The regularity of the serum penicillin curves is apparent in Figure 1. At low dosages the serum concentration was almost linearly related to the amount of penicillin injected. Thus, one hour after dosages of 0.15, 0.3, 0.6, 1.5, 3 and 10 mg./Kg., the blood levels were 0.095, 0.17, 0.38, 1.1, 3.5 and 11.3 micrograms per cc. respectively. At all dosages the serum concentrations fell off at the same initial rate of approximately 70 per cent per hour¹⁵ (i.e., 70 per cent of the residual penicillin disappeared each succeeding hour). After the first few hours, however, the serum concentrations fell off more slowly. This is evident in the curves obtained in patients who had received large doses of penicillin (top curves of Fig. 1) and may perhaps be related to the fact that at these high dosages a significant reservoir of penicillin is established in the tissues soon after its injection. When, because of the rapid urinary excretion, the plasma concentration of diffusible penicillin falls below that in the tissues, the direction of flow is probably reversed. The diffusion of penicillin out of the tissues into the blood may then serve to maintain the plasma concentration at significantly higher levels than would otherwise have been the case.^{12,14,16}

Whatever the explanation, it is evident in Figure 1 that after large doses of penicillin the serum concentration is regularly higher than one would anticipate from the dif-

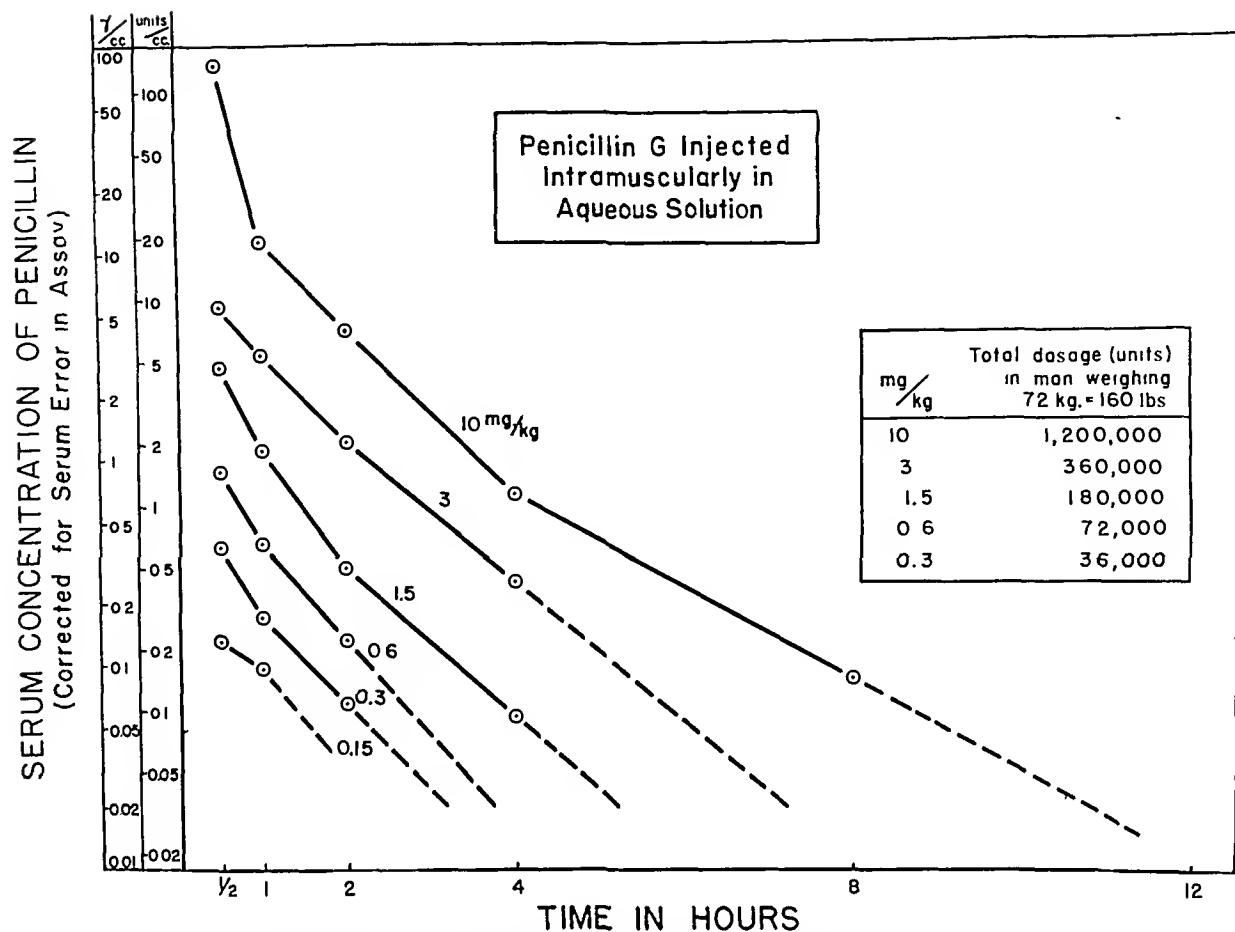


FIG. 1. The serum concentrations of penicillin G in man after its intramuscular injection in aqueous solution. Each value in the figure is the median of at least ten patients, as indicated in Table 1A.

TABLE 1
SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION IN AQUEOUS SOLUTION

Dosage, Mg./Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection					Time in Hours after Single Injection				
		Mg.	Units	1/2	1	2	4	8	1/2	1	2	4	8
				Serum Concentrations in Micrograms per cc. (Median)					Serum Concentrations in Units per cc. (Median)				
10.00	10	720	1,200,000	17.9	11.3	4.4	0.67	0.085	29.9	18.9	7.3	1.1	0.14
3.0	10	216	360,000	5.6	3.5	1.2	0.25	<0.015	9.4	5.9	2.1	0.42	
1.5	16	108	180,000	2.8	1.1	0.3	0.055	<0.015	4.7	1.8	0.5	0.092	
0.6	16	43	72,000	0.87	0.38	0.13	<0.015		1.5	0.63	0.21		
0.3	10	22	36,000	0.37	0.17	0.065	<0.015		0.62	0.28	0.11		
0.15	10	11	18,000	0.13	0.095	<0.015			0.22	0.16			

TABLE 1A

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN THE SERUM CONCENTRATION OF PENICILLIN G FOLLOWING INTRAMUSCULAR INJECTION IN AQUEOUS SOLUTION

Dosage, Mg./Kg.	No. Patients		Time in Hours					
			$\frac{1}{2}$	1	2	4	8	12
			Serum Concentrations in Micrograms per cc.					
10	10	Median	17.9	11.3	4.35	0.67	0.085	<0.015
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	21.2 11.1	17.6 6.0	6.4 1.67	1.33 0.21	0.21 <0.015	
		σ Med.	3.63	3.42	2.02	0.41	0.068	
		Standard Error	0.79	0.77	0.46	0.09	0.017	
3	10	Median	5.55	3.5	1.23	0.25		
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	12.0 3.75	5.5 1.8	4.0 0.3	0.83 0.1		
		σ Med.	2.48	1.31	0.56	0.21		
		Standard Error	0.58	0.29	0.23	0.05		
1.5	16	Median	2.8	1.1	0.3	0.055		
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	9.6 1.6	3.2 0.66	0.65 0.16	0.13 >0.015		
		σ Med.	2.1	0.87	0.16	0.039		
		Standard Error	0.41	0.17	0.032	0.01		
0.6	16	Median	0.87	0.38	0.13			
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	1.4 0.33	0.62 0.15	0.2 0.081			
		σ Med.	0.34	0.17	0.036			
		Standard Error	0.071	0.036	0.006			
0.3	10	Median	0.37	0.17	0.065			
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	0.41 0.25	0.29 0.11	0.065 <0.011			
		σ Med.	0.044	0.08	0.045			
		Standard Error	0.01	0.018	0.013			
0.15	10	Median	0.13	0.095				
		Range $\left\{ \begin{array}{l} \text{High} \\ \text{Low} \end{array} \right.$	0.27 0.1	0.12 0.05				
		σ Med.	0.065	0.063				
		Standard Error	0.02	0.017				

σ Med. = Standard deviation of median.

TABLE II

SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION OF SUSPENSIONS IN PEANUT OIL AND BEESWAX
(LOTS A, B AND C RAPIDLY ABSORBED)

Dos- age, Mg./ Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection								Time in Hours after Single Injection							
				½	1	2	4	8	12	24	½	1	2	4	8	12	24		
		Mg.	Units	Serum Concentrations in Micrograms per cc. (Median)								Serum Concentrations in Units per cc. (Median)							
10.0	9	720	1,200,000	2.0	4.0	6.0	5.23	2.4	0.98	0.098	3.4	6.66	10.0	8.70	4.0	1.62	0.16		
3.0	13	216	360,000	0.5	0.6	0.89	0.87	0.4	0.28	0.085	0.84	1.0	1.5	1.4	0.67	0.47	0.14		
1.5	12	108	180,000	0.45	0.47	0.53	0.33	0.26	0.12	<0.015	0.75	0.78	0.88	0.55	0.43	0.2			

TABLE IIA

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN SERUM CONCENTRATION OF PENICILLIN G FOLLOWING ADMINISTRATION IN PEANUT OIL-BEESWAX SUSPENSION (LOTS A, B AND C RAPIDLY ABSORBED)

Dosage, Mg./Kg.	No. Patients		Time in Hours						
			1/2	1	2	4	8	12	24
			Serum Concentrations in Micrograms per cc.						
10	9	Median	2.0	4.0	6.0	5.23	2.4	0.98	0.098
		Range { High Low	6.7 1.4	6.7 2.4	8.8 3.0	10.0 2.5	4.8 0.3	2.5 0.045	0.19 <0.015
		σ Med.	1.87	1.21	1.61	2.17	1.25	0.81	0.058
		Standard Error	0.5	0.29	0.38	0.54	0.34	0.19	0.015
3	13	Median	0.5	0.6	0.9	0.87	0.4	0.28	0.085
		Range { High Low	0.62 0.28	1.0 0.31	1.25 0.12	1.6 0.26	0.91 0.13	1.04 <0.015	0.16 <0.015
		σ Med.	0.11	0.27	0.13	0.36	0.26	0.3	0.035
		Standard Error	0.025	0.06	0.07	0.081	0.057	0.067	0.009
1.5	12	Median	0.45	0.47	0.53	0.33	0.26	0.12	<0.015
		Range { High Low	0.63 0.015	1.6 <0.015	2.0 <0.015	2.2 0.128	0.75 <0.015	0.21 <0.015	
		σ Med.	0.26	0.5	0.75	0.62	0.21	0.055	
		Standard Error	0.045	0.011	0.16	0.13	0.057	0.22	

ference in dosage, assuming a linear relationship. It is pertinent to note that, in general, it required a 2.5- to 10-fold increase in the dosage of penicillin in order to prolong a given plasma level by one hour. This merely reflects the rapid excretion of the drug. An increase in the dosage per

cussion of these factors is not within the scope of this paper.^{13,14}

BLOOD LEVELS AFFORDED BY PENICILLIN G IN PEANUT OIL-BEESWAX SUSPENSION

The median serum levels of penicillin following the administration of penicillin G

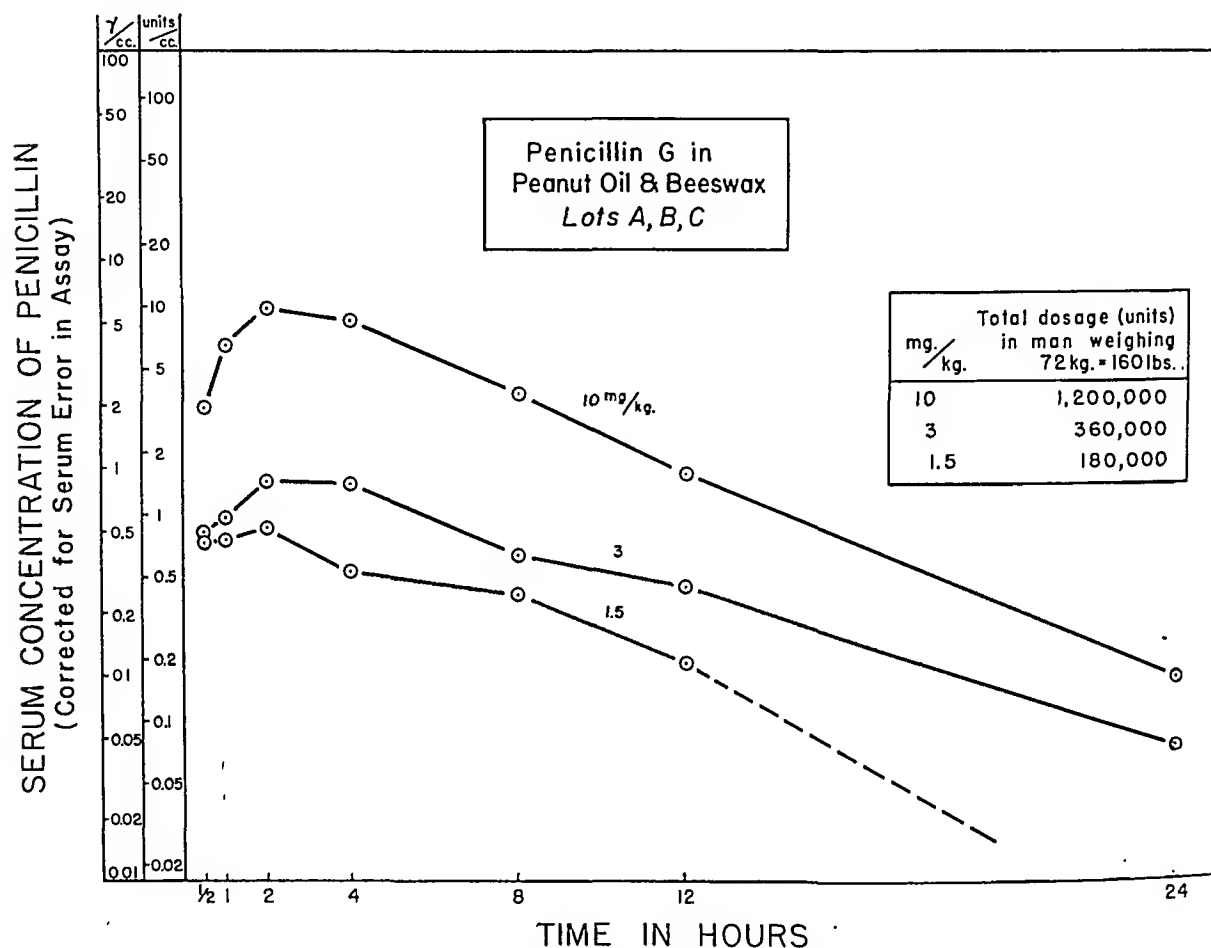


FIG. 2. The serum concentrations of penicillin G in man after the intramuscular injection of suspensions in peanut oil and beeswax. Each value in the figure is the median of nine to thirteen patients injected with easily absorbed preparations (Lots A, B and C).

injection is obviously a wasteful method of prolonging the time of action of penicillin; but in the sick patient, it is perhaps preferable to the administration of repeated small injections. The choice between (1) a small number of relatively large injections, (2) a large number of small injections and (3) a suspension of penicillin in oil and beeswax involves a number of factors (e.g., cost of penicillin, cost of hospitalization, physical condition of the patient, desirability of ambulatory treatment, etc.). The dis-

in peanut oil-beeswax (pooled data for three of the four lots tested) are given in Table II, Table IIA and Figure 2. As has been found by numerous previous workers, the highest serum level was not attained for several hours after administration and the peak concentrations were lower than after a corresponding dose of the aqueous product. The slower absorption of penicillin was further reflected in the slow rate of fall of the serum concentration and in the long period of time for which penicillin remained

in the serum at measurable levels. Thus, seven of eight patients given 10 mg./Kg. had measurable levels twenty-four hours after the injection, and at a dosage of 3 mg./Kg., eight of eleven then had measurable concentrations. After an injection of

a degree of variation comparable to that observed in patients receiving the aqueous solutions; however, thereafter at every dosage level and with every preparation used there was a much greater degree of variation. (Table IIA.)

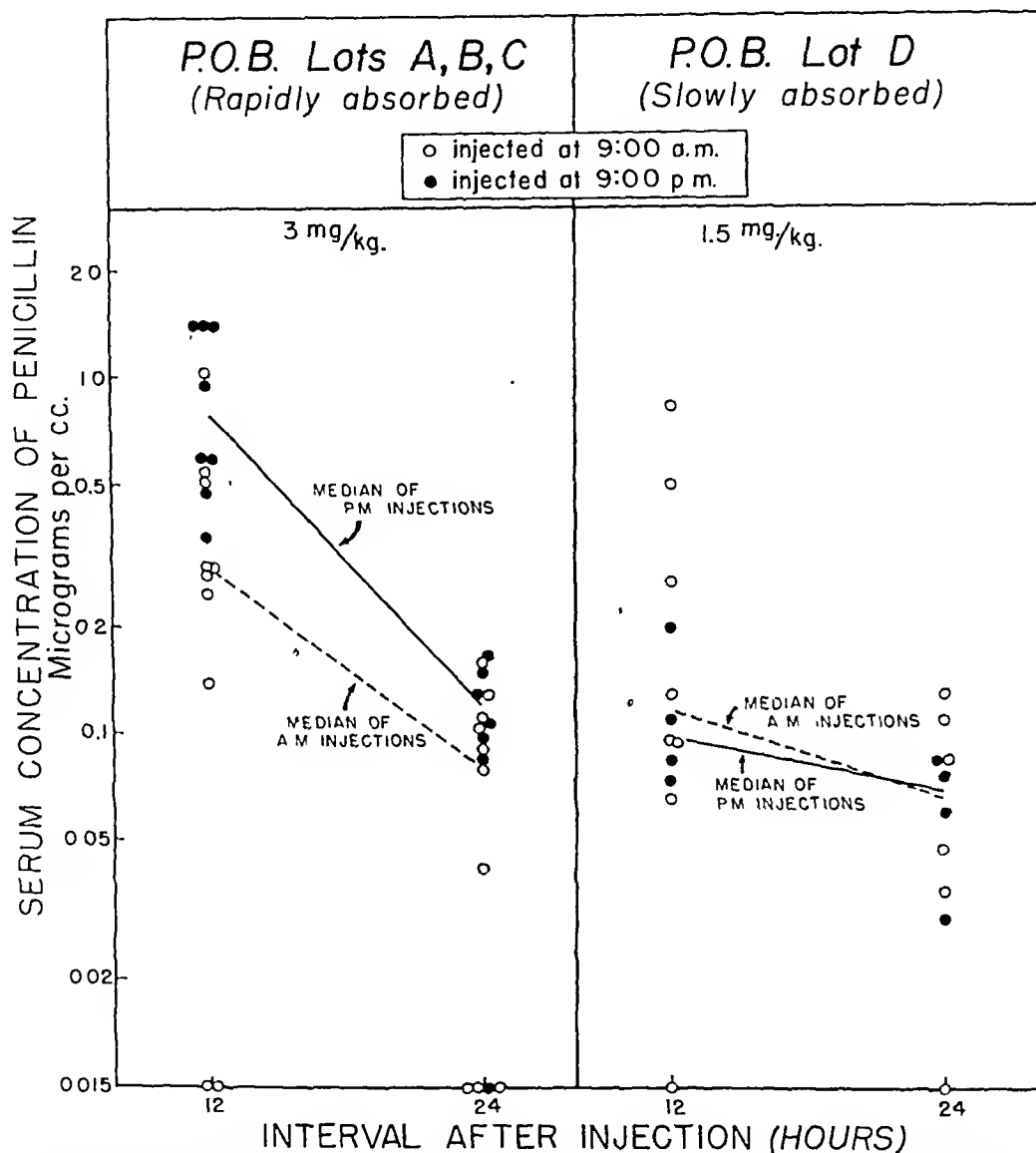


FIG. 3. The effect of time of administration on the twenty-four-hour serum levels following injection of rapidly absorbed (Lots A, B, C) and slowly absorbed (Lot D) preparations of penicillin G in peanut oil and beeswax. The lines indicate the median values in each group of patients.

1.5 mg./Kg., however, only four of seven twelve-hour sera and none of the twenty-four-hour sera contained measurable quantities of penicillin.

For the first eight to twelve hours the serum levels in patients given these particular peanut oil-beeswax suspensions showed

In confirmation of Romansky,¹⁷ when injections were given at 9 P.M. instead of 9 A.M., consistently higher levels were observed after twelve and twenty-four hours. (Fig. 3.) This presumably reflects the fact that in the sleeping patient the site of injection is not massaged as vigorously as it is in

the waking patient. A smaller proportion is then absorbed during the first twelve-hour period, making for higher levels subsequently. (It is significant in this regard that a more recent lot of penicillin which was apparently absorbed more slowly, and

series of additional patients was then run for more critical comparison, with results shown in Figure 4, Table III and Table IIIA.

This particular lot was evidently absorbed more slowly than those previously used, the serum concentration reaching a peak value

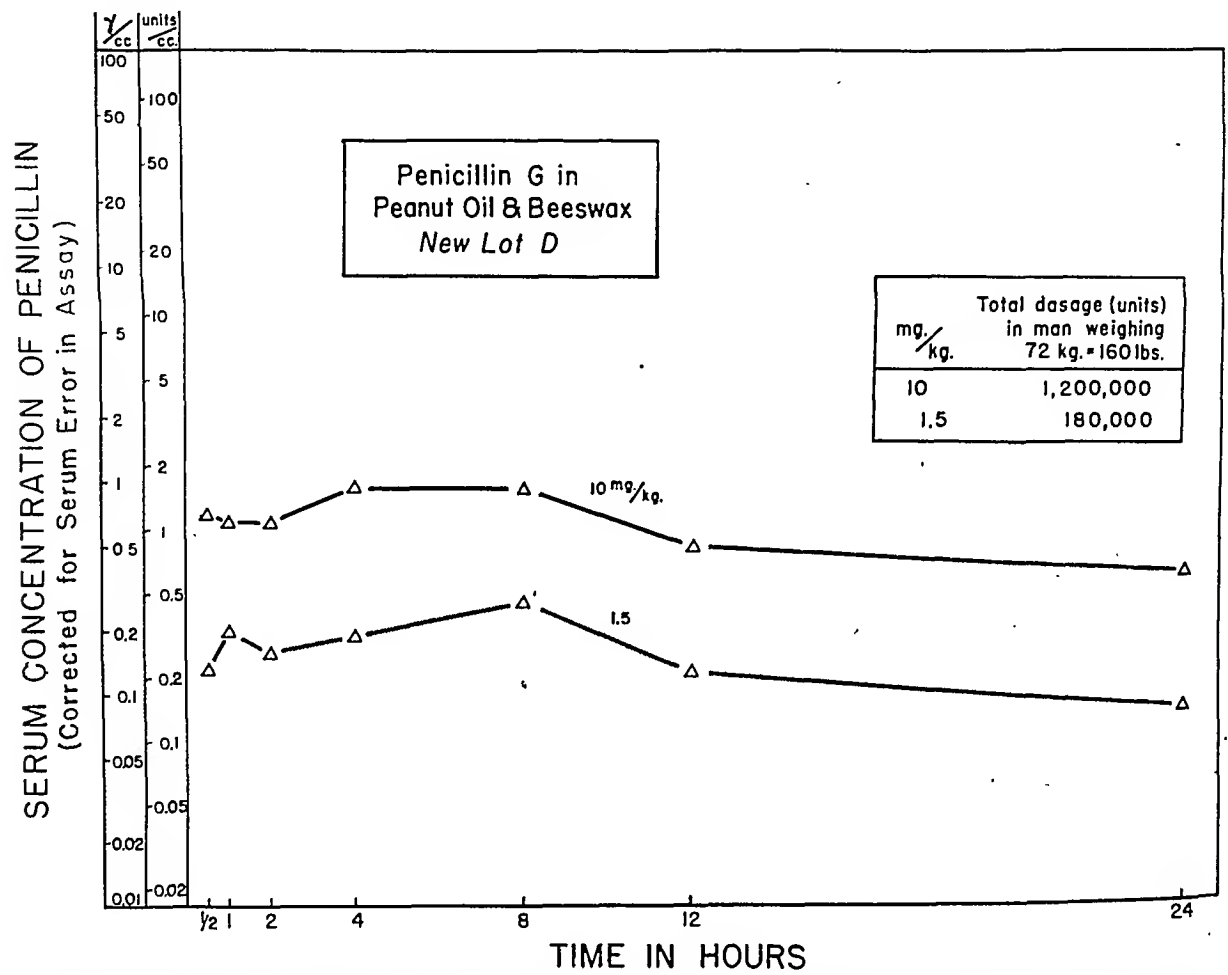


FIG. 4. The serum concentrations of penicillin G in man after the intramuscular injection of a suspension in peanut oil and beeswax. Each value in the figure is the median of six to eight patients injected with a slowly absorbed preparation (Lot D).

which gave much more sustained levels than the three lots previously discussed, did not show this difference between the morning and evening injections. (Fig. 3.)

One recent commercial lot of the peanut oil-beeswax material, here designated as Lot D, gave results which differed materially from those obtained with the three preparations previously used. It was first noted that this lot provided distinctly higher twenty-four-hour serum concentrations. A

after four to eight hours instead of two hours. That peak value was uniformly lower (after 10 mg./Kg. the median peak concentration was 0.95 micrograms per cc. instead of 6.0 micrograms per cc. as with the other penicillin suspensions tested). More important, however, was the fact that the serum penicillin level thereafter fell off far more slowly so that the median serum concentration twenty-four hours after injection was 5.5 to 7.5 times higher than that

afforded by the other preparations injected in equal dosage. Thus, at 1.5 mg./Kg., five of eight patients receiving Lot D had meas-

of any of six patients receiving 1.5 mg./Kg., and levels of approximately 0.1 micrograms were attained only after the administration

TABLE III

SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION OF SUSPENSIONS IN PEANUT OIL AND BEESWAX
(LOT D SLOWLY ABSORBED)

Dosage, Mg./Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection							Time in Hours after Single Injection						
				½	1	2	4	8	12	24	½	1	2	4	8	12	24
		Mg.	Units	Serum Concentrations in Micrograms per cc. (Median)							Serum Concentrations in Units per cc. (Median)						
10	6	720	1,200,000	0.71	0.65	0.65	0.95	0.95	0.50	0.54	1.18	1.08	1.08	1.60	1.60	0.83	0.9
1.5	8	108	180,000	0.13	0.20	0.16	0.19	0.28	0.13	0.085	0.21	0.33	0.27	0.32	0.47	0.21	0.14

TABLE IIIA

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN THE SERUM CONCENTRATION OF PENICILLIN G FOLLOWING ADMINISTRATION IN PEANUT OIL-BEESWAX SUSPENSION
(LOT D SLOWLY ABSORBED)

Dosage, Mg./Kg.	No. Patients		Time in Hours						
			½	1	2	4	8	12	24
			Serum Concentrations in Micrograms per cc.						
10	6	Median	0.71	0.65	0.65	0.95	0.95	0.5	0.54
		Range { High Low	2.4 0.5	2.4 0.15	2.7 0.11	3.0 0.1	1.0 0.3	1.0 0.12	0.6 0.1
		σ Med.	1.06	0.99	1.54	1.08	0.38	0.33	0.25
		Standard Error	0.31	0.28	0.49	0.31	0.12	0.095	0.08
1.5	8	Median	0.13	0.2	0.16	0.19	0.28	0.13	0.085
		Range { High Low	0.55 <0.015	0.25 <0.015	0.16 <0.015	1.0 0.03	0.96 0.043	0.51 <0.015	0.13 <0.015
		σ Med.	0.23	0.19	0.18	0.18	0.27	0.33	0.076
		Standard Error	0.057	0.057	0.048	0.045	0.068	0.088	0.002

urable levels after twenty-four hours, averaging 0.08 micrograms per cc. With the other preparations no penicillin had been found after twenty-four hours in the serum

of 3 mg./Kg. Finally, reflecting the slow absorption of Lot D and the shape of its serum-penicillin curves, it made no significant difference in the magnitude of the

twelve- and twenty-four-hour serum levels whether the material was injected in the morning or evening. (Fig. 3.)

Assays of aqueous extracts showed that all four lots studied contained the amount of penicillin indicated on the labels. It

TABLE IV
FREQUENCY WITH WHICH A GIVEN DOSE OF PENICILLIN G IN AQUEOUS SOLUTION MUST BE INJECTED IN ORDER TO MAINTAIN A DESIRED PLASMA LEVEL.

				To Maintain a Plasma Concentration of Penicillin G in Excess of									
Micrograms per cc Oxford Units per cc				0.1	0.2	0.5	1.0	2.0	5.0	10.0			
				0.16	0.32	0.8	1.6	3.2	8.0	16.0			
Dosage per Kg		Total Dose in Average Adult		The Injections Indicated in the Left Hand Column Should Be Repeated at the Intervals (Hours) Indicated below in the Body of the Table.									
Mg.	Units	Mg.	Units										
10	16,700	720	1,200,000	8.0	6.0	4.5	3.5	3.0	2.0	1.2			
3	5,000	216	360,000	5.0	4.0	3.0	2.0	1.6	0.6				
1.5	2,500	108	180,000	3.0	2.5	1.7	1.2	0.8					
0.6	1,000	43	72,000	2.0	1.5	0.8							
0.3	500	22	36,000	1.6	0.9								
0.15	250	11	18,000	0.9									

seems clear that as yet undefined factors (e.g., particle size of the beeswax, particle size of the penicillin and the fluidity of the mixture) may affect the rate of absorption to an extraordinary degree, evidenced both in the maximum serum concentration afforded by a given dosage and in the length of time for which the penicillin remained in the plasma and tissues at measurable levels.

DOSAGE AND FREQUENCY OF INJECTION NECESSARY TO SUSTAIN PLASMA CONCENTRATIONS OF PENICILLIN G AT A GIVEN LEVEL

From the data of Table i and Figure 1 one can by interpolation construct tables which indicate (1) how often a given dose of penicillin must be repeated or (2) what dose of penicillin must be administered at fixed intervals in order to keep the plasma concentration above a certain level (similar studies by Fleming et al.,⁵ Rammelkamp and Kirby⁹). These data are given in Tables iv and v which may perhaps serve

as guides to treatment. Thus, if the physician chooses to fix the amount of penicillin administered per injection and to vary the frequency of its administration, Table iv indicates how often that fixed dose should be repeated in order to provide a desired plasma level. If instead the physician wishes to keep the interval between injections fixed, then Table v indicates the dosages of penicillin which must be given at each injection in order to provide a given level for the entire interim period.

For purposes of illustration, in a patient with a staphylococcal septicemia in which the causative organism is shown to be sensitive to 0.02 micrograms of penicillin per cc. and to be killed at a maximal rate at a concentration of 0.096 micrograms, the physician may wish to maintain the plasma level at 0.2 micrograms per cc. (Present information indicates that the plasma level should be somewhat higher than the level desired in the tissues although the precise differential depends on many factors which cannot be considered in detail^{13,14} and which will obviously vary from organ to organ.) In the second vertical column of Table iv alternative methods for maintaining that desired concentration are listed. A dosage of 10 mg./Kg. (1,200,000 units in the average adult) may be given every six hours, 3.0 mg./Kg. may be given every four hours, 1.5 mg./Kg. given every two and five-tenth hours, 0.6 mg./Kg. given every one and five-tenth hours or 0.3 mg./Kg. every hour. All these schedules of treatment would maintain the serum concentration at or above 0.2 micrograms per cc.

It is important to note that these intervals between injections could be appreciably lengthened and perhaps even doubled without prejudicing the outcome of treatment.^{13,14} Only the total time required to effect cure might thereby be prolonged.

Again for purposes of illustration, had the organism been a strain of *Streptococcus fecalis*, which is killed *in vitro* only by concentrations in excess of 1.0 microgram per cc. and for which 4 micrograms per cc.

provides the maximal rate of killing, one might desire to maintain serum concentration of, e.g., 10 micrograms per cc. As seen in Table iv, it would be necessary to inject 10 mg./Kg. every hour to maintain this level. Since this represents 1,200,000 units

e.g., 0.5 microgram per cc. If the interval between injections is to be fixed at four hours, the third vertical column shows that the required dose would be 7 mg./Kg. or a total of 850,000 units in the average adult. Should the interval between inje-

TABLE V

AMOUNT OF PENICILLIN G IN AQUEOUS SOLUTION WHICH MUST BE INJECTED AT GIVEN INTERVALS IN ORDER TO MAINTAIN A DESIRED PLASMA LEVEL

Interval between Injections (Hours)	To Maintain a Plasma Concentration of Penicillin G in Excess of							Micrograms per cc.
	0.1	0.2	0.5	1.0	2.0	5.0	10.0	
	0.16	0.32	0.8	1.6	3.2	8.0	16.0	Units per cc.
The Following Dosages Must Be Given at the Intervals Indicated in the Left Hand Column. (Upper left hand figure in each block is dosage in mg./Kg.; lower right hand figure is the total dose in units in average adult.)								
1	0.16 20,000	0.35 40,000	0.74 85,000	1.3 150,000	2.1 250,000	4.2 500,000	9.1 1,000,000	
2	0.45 50,000	0.95 100,000	1.9 220,000	2.7 330,000	4.7 550,000	11.5 1,300,000		
3	1.2 140,000	1.9 220,000	2.9 340,000	5.7 675,000	11.5 1,300,000			
4	2.0 235,000	2.8 330,000	7.4 855,000	11.4 1,300,000				
6	5.2 600,000	8.8 1,000,000						
8	12.0 1,400,000							

in a patient weighing 72 Kg., continuous intravenous or intramuscular administration designed to maintain a level of 10 micrograms per cc. would probably be the method of choice.¹³

If circumstances dictate a fixed interval between injections, e.g., every four hours, the data of Table v are applicable. In a patient with a severe pneumococcal pneumonia due to an organism sensitive to 0.016 micrograms per cc. and killed at a maximal rate by a concentration of 0.096 micrograms per cc., one might wish the serum concentration to be maintained at,

tions be set at two hours, column three shows that only 1.9 mg./Kg. would be required to achieve the same effect, the individual dose representing 220,000 units in the average adult. Because of the wide margin of safety afforded by the time required for organisms to recover from the effects of penicillin, plus the body's own defense mechanisms, plus the possible persistence of penicillin in the tissues,^{12,14} smaller doses than these or longer time intervals would also be effective even if they did not provide a concentration maintained at the most effective level; at the

smaller dosages, however, the total time required to effect cure might be significantly prolonged.

SUMMARY

1. Serum penicillin levels were studied in 138 patients following the intramuscular injection of a single dose of crystalline sodium penicillin G in aqueous solution or in peanut oil-beeswax suspension.

2. The aqueous solution was given at six dosage levels (0.15, 0.3, 0.6, 1.5, 3.0 and 10.0 mg./Kg.), totalling 18,000 to 1,200,000 units in the average adult. The median serum concentrations one-half, one, two, four, eight and twelve hours after the administration of penicillin at these varying dosages have been calculated and the pharmacologic significance of the resulting curves discussed.

3. Peanut oil-beeswax mixtures were given in dosages of 1.5, 3.0 and 10.0 mg./Kg. The high degree of variation in individual lots precluded a discussion of average or median serum concentrations provided by the preparations currently available.

4. Tables are presented which enable the physician to determine either the frequency at which a given dose should be injected or the dosage of penicillin which should be given at stated intervals in order to maintain a given concentration of penicillin in the plasma.

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Streptomycin*

A Clinical Study of Its Use in Twenty-six Cases

WALTER S. PRIEST, M.D. and JAMES B. O'NEILL, M.D.

Chicago, Illinois

WAKSMAN and Schatz¹ have reviewed the origin, production and assay, biologic and chemical properties, action, pharmacology and toxicity of streptomycin. Their *in vitro* experiments indicated that, depending on its concentration, the drug possesses both bacteriostatic and bactericidal action against many gram-negative and gram-positive organisms. Animal experiments showed its ability to control infections with organisms of the *Salmonella*, *Brucella* and *Hemophilus* groups. Herrell and Nichols² reported the results of the clinical use of streptomycin in forty-five infections which included those due to *Escherichia coli*, *Eberthella typhosa*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Proteus ammoniae*, *Klebsiella pneumoniae* and *Hemophilus influenzae*.

In this paper we are summarizing the results obtained with streptomycin in the treatment of urinary tract infections, septicemia due to *Escherichia coli*, brucellosis, and *Hemophilus influenzae* meningitis.† The use of streptomycin in three cases of subacute bacterial endocarditis caused by penicillin-resistant strains of streptococci has previously been reported.³

URINARY TRACT INFECTIONS

There are nineteen cases of urinary tract infections. (Table I.) *Escherichia coli* and *Pseudomonas aeruginosa*, either alone or in

† This investigation was under the auspices of, and the streptomycin furnished by, the Committee on Chemotherapeutics and Other Agents of the National Research Council.

* From the Department of Medicine, Wesley Memorial Hospital, Northwestern University Medical School, Chicago, Ill.

combination, were the organisms encountered. The patients were selected either because previous therapy with other agents had been ineffective or because of the acuteness and severity of the infection. Excluding Case 2, the average duration of treatment was six days. The dosage of streptomycin in most cases was 0.15 Gm. intramuscularly every three hours, a total of 1.2 Gm. each twenty-four hours. Both streptomycin hydrochloride and the sulfate were used; no difference in therapeutic efficiency could be detected. This dosage was considered satisfactory inasmuch as the urinary concentrations of streptomycin invariably exceeded 100 micrograms per cc. This concentration was found by Helmholz⁴ to be adequate for inhibiting growth of bacteria in urine. Only infections due to gram-negative bacteria were treated and most of these were due to a single organism. The results were considered good in all but three cases. In Case 2, the urinary tract infection complicated a rather "brittle" case of diabetes mellitus. After fifty-five days of treatment, during which time 85 Gm. were administered, the urine still contained pus, and cultures were positive for *E. coli* despite the fact that urine streptomycin levels of over 1,500 micrograms per cc. were obtained by the daily administration of 4.0 Gm. of the drug. In Case 16, the urinary infection was associated with a ureteral calculus, and the urine was not rendered free of bacteria or pus although the urine streptomycin levels

TABLE 1
GENITOURINARY INFECTIONS TREATED WITH STREPTOMYCIN

Case No.	Type of Infection	Causative Organism	Days of Therapy	Total Dose Gm.	Route of Administration	Clinical Result
1	Pyelonephritis	Esch. coli	8	12.0	Intramuscular	Good; urine sterile in 48 hours
2	Pyelonephritis, cystitis	Esch. coli	55	85.0	Intramuscular Intravenous	Poor; Esch. coli and pyuria persisted in spite of intensive therapy; concomitant diabetes mellitus
3	Cystitis	Esch. coli	5	6.2	Intramuscular	Good; culture negative in 5 days
4	Pyelocystitis, left ureteral calculus	Ps. aeruginosa	7	7.5	Intramuscular	Good; urine culture negative in 72 hours
5	Cystitis	Esch. coli	5	6.6	Intramuscular	Good; urine culture negative in 96 hours
6	Pyelonephritis, hydronephrosis, nephrolithiasis	Ps. aeruginosa Esch. coli	5	5.6	Intramuscular	Good; cultures negative in 72 hours
8	Cystitis	Esch. coli	3	3.0	Intramuscular	Good; urine culture negative 5 days after therapy begun
9	Pyelonephritis	Esch. coli Ps. aeruginosa	3	4.0	Intramuscular	Good; nephrostomy done; urine negative in 5 days; associated diabetes mellitus
10	Pyelonephritis, cystitis	Esch. coli	8	10.6	Intramuscular	Good; urine negative after 7 days treatment
11	Cystitis, pyelonephritis	Esch. coli	7	8.8	Intramuscular	Good; urine culture negative 10 days following institution of therapy
12	Cystitis, pyelonephritis	Esch. coli	4	4.8	Intramuscular	Good; urine culture negative in 5 days
13	Perinephric Abscess	Ps. aeruginosa Alk. faecalis	12	15.7	Intramuscular	Good; abscess complication of nephrolithotomy; concurrent penicillin treatment
14	Cystitis	Esch. coli	9	11.9	Intramuscular	Good; urine culture negative in 4 days
15	Pyelitis, cystitis	Esch. coli	5	5.8	Intramuscular	Good; urine culture negative in 3 days; concurrent treatment with sulfasuxidine
16	Pyelitis, cystitis	Esch. coli	6	6.3	Intramuscular	Poor; infection associated with left renal calculus; Esch. coli persisted
17	Cystitis, pyelonephritis	Ps. aeruginosa	12	10.0	Intramuscular	Poor; Ps. aeruginosa persisted; associated diabetes mellitus
20	Pyelitis, cystitis	Esch. coli	7	9.0	Intramuscular	Good; associated prostatism; Rx with indwelling catheter; urine culture negative in 7 days
22	Cystitis	Esch. coli	6	6.0	Intramuscular	Good; urine negative in 6 days
23	Cystitis, pyelonephritis	Esch. coli	3	4.0	Intramuscular	Good; concurrent therapy with sulfasuxidine

ranged between 200 and 400 micrograms per cc.

The following two case reports illustrate the usual course of the successfully treated patients:

CASE 1. A male, age fifty-two, had general malaise, moderate anorexia, weakness, frequency of urination, nocturia and dysuria following a sore throat and tooth extraction one month prior to admission. Physical examination revealed nothing significant except hyperten-

sion. His blood pressure was 180/110, temperature 98.6°F. The erythrocyte count was 3,910,000, hemoglobin 14 Gm., leukocyte count 9,850, differential normal. Blood urea nitrogen was 59, creatinine 5.9 mg. per cent. Urinalysis showed albumin, many pus cells and a few hyaline and granular casts. Following an intravenous pyelogram, the patient developed a fever of 102°F., the urine became purulent and culture revealed a heavy growth of *Escherichia coli*. Penicillin and urotropin were administered without effect on the fever. The amount of

pus in the urine steadily increased until it constituted approximately 50 per cent of the specimen.

At this point streptomycin in dosage of 0.15 Gm. intramuscularly every three hours was started. The response was dramatic. Within forty-eight hours the urine had become clear and cultures were negative. Fever, urinary frequency and dysuria subsided rapidly. The blood urea nitrogen declined to 34.8 and creatinine to 2.3 mg. per cent. Later the urine contained an occasional pus cell and cultures showed a light growth of a gram-positive diplococcus which disappeared under penicillin therapy. While receiving streptomycin, the patient developed a troublesome pruritus and a diffuse rash which subsided when the drug was discontinued.

In this case the prompt clearing of the urinary infection was undoubtedly due to streptomycin. Duration of therapy was eight days; the total dose was 12.0 Gm. of the sulfate.

CASE 15. A female, age forty-nine, developed fever, dysuria, frequency, nocturia and pain in the left lower quadrant of the abdomen radiating to the anterior and medial aspects of the left thigh two days prior to admission. A similar episode diagnosed as "cystitis" had occurred twelve years previously. Physical examination was normal except for tenderness in the left costovertebral area. Her temperature was 99.8°F., pulse 86, respirations 20 per minute. Except for a few pus cells in the urine, the findings were normal. Cystoscopic examination revealed a few small, degenerating cysts in the bladder wall. The ureteral orifices were hyperemic and edematous bullae were present. A diagnosis of subacute cystitis and ascending infection of the ureters and renal pelves was made. Urine cultures revealed a heavy growth of *Escherichia coli*.

Streptomycin was administered, 1.2 Gm. of the sulfate intramuscularly in dosage of 0.15 Gm. every three hours. Symptoms subsided within forty-eight hours and the patient remained asymptomatic during the remainder of her hospital stay of ten days. A total of 5.8 Gm. of

streptomycin was given. Urine cultures were negative on the third day of streptomycin therapy. Intramuscular administration of streptomycin produced severe pain at the sites of injection. Moist dressings were required for relief. Upon discontinuance of streptomycin, sulfasuxidine was given in dosage of 2.0 Gm. four times daily. The patient has remained asymptomatic for nine weeks and the urine has remained clear.

BRUCELLOSIS

Live et al.⁵ reported that streptomycin exerted a definite bacteriostatic effect on experimental *Brucella abortus* infections in guinea pigs. Herrell and Nichols² administered streptomycin to three patients during the acute, febrile stages of severe undulant fever but considered the results good in only one instance. In this case the spleen was considered to be a focus of reinfection and splenectomy was performed, following which the patient made a rapid recovery. They reported discouraging results in the treatment of chronic brucellosis. Three patients were treated by us; two cases were acute in which the result was apparently satisfactory, and one was chronic in which the result was discouraging. Abstracts of these three cases follow:

CASE 7. E. S., a female, age thirty-seven, developed fever, which at times reached 104°F., headaches, hot flushes and profuse night sweats three weeks after returning from a trip to Mexico. She was given sulfathiazole for five days without beneficial effect upon her subjective symptoms although the fever peaks were lowered to 101° and 102°F. Because of the persistence of symptoms she was hospitalized. Physical examination was normal. The spleen was not palpable. The erythrocyte count was 5.55 million, hemoglobin 14.0 Gm., leukocyte count 5,650 with a relative lymphocytosis of 75 per cent. The sedimentation rate was 24 mm. in one hour. Serum agglutination tests against members of the *Eberthella*, *Salmonella* and *Proteus* groups were negative. Against *Brucella abortus*, agglutination was 2 plus in a dilution

of 1:1280. The brucellergin skin test was 4 plus positive. Four blood cultures were negative for members of the *Brucella* group. It was believed that, even in the absence of a positive blood culture, a diagnosis of acute brucellosis was justified and streptomycin was given in dosage of 0.5 Gm. every three hours for two days, 0.25 Gm. every three hours for two days, and 0.125 Gm. every three hours for nine days, a total of 45 Gm. in sixteen days. During the first three days of therapy, the maximum temperature was 101.6°F.; during the next five days it was 99.6°F., after which it remained normal. After the third day of treatment, she was asymptomatic except for occasional slight night sweats which ceased within a week. The patient has been asymptomatic for ten weeks.

Perhaps the apparently good result in this case resulted from the large daily dosage given at the outset of therapy together with continuance of therapy well into convalescence. We realize that in this disease a follow-up period of ten weeks is inadequate for a final conclusion regarding therapy. Harris⁶ is of the opinion that while streptomycin may cause prompt relief of the acute stage and even produce negative cultures of blood, a relapse is likely unless local or splenic foci of infection can be removed. Subjectively the patient felt "cured" within seventy-two hours.*

The other case of acute brucellosis (Case 19) was that of a male, age forty-three, a meat trimmer, who had been ill approximately six weeks prior to admission to the hospital. Fever of the intermittent type was present. Serum agglutination was 2 plus positive against *Br. bovinis* in dilution of 1:640 and *Br. melitensis* in dilution of 1:320. The brucellergin skin test was 4 plus positive (0.04 cc.). The spleen was palpable. Repeated cultures of blood were negative. Streptomycin was administered intramuscularly as follows: 0.4 Gm. every three hours for two days; 0.2 Gm. every three hours for two days; omitted one day; 0.4 Gm. every

three hours for nine days. At this point the temperature was normal, the spleen was no longer palpable and the patient felt well. After eleven days of normal temperature he was discharged. Four weeks later there were no signs of recurrence.

The result in the third case of brucellosis coincides with the experience of Herrell and Nichols² and Harris⁶ in treating the chronic form of the disease.

CASE 21. A male, age forty-three, had acquired brucellosis in 1941 at which time he was hospitalized for three months. Blood cultures were positive for *Brucella abortus*. Treatment consisted of foreign protein which resulted in formation of abscesses at the sites of injection. Following this he felt improved but did not regain his former state of well being. For the next three years he was able to work only a few hours each day. He always felt weak and tired and considered his efficiency greatly impaired. In 1944, he was treated with brucellin, after which a temporary improvement was noted only to be followed by periods of extreme fatigue, lassitude and drenching, encraving night sweats. No definite abnormalities were found on physical examination. The brucellergin skin test was 4 plus positive. The erythrocyte count was 3,990,000, hemoglobin 14.0 Gm., leukocyte count 6,000, with a normal differential. Serum agglutination against *Brucella abortus* was 2 plus in a dilution of 1:160. The sedimentation rate was 11 mm. in one hour. A chest x-ray was normal. Streptomycin was administered intramuscularly as follows: 0.3 Gm. of sulfate every three hours for seven days; 0.2 Gm. every three hours for two days; 0.15 Gm. every three hours for two days; 0.1 Gm. every three hours for eight days, a total dose of 28.8 Gm. in nineteen days. Except for an occasional rise in temperature to 100° and 101°F. (rectally) there was no change in the patient's condition. The symptoms of weakness, etc., remained. The results of therapy were poor.

INFLUENZAL MENINGITIS

Herrell and Nichols² obtained cures in four cases of meningitis due to *Hemophilus*

* Since this paper was submitted, ten months have elapsed since the patient was discharged from the hospital. She has remained asymptomatic.

influenzae. One of these patients died two months later of post-meningitis hydrocephalus. Buttre et al.⁶ reported a case of influenzal meningitis in which the patient was successfully treated with streptomycin, sulfadiazine and antiserum. There are two cases of meningitis due to *H. influenzae* in our series.

CASE 25. The diagnosis of influenzal meningitis was confirmed by culture of the spinal fluid in a male infant, age seven months. Streptomycin was not started until the fiftieth day of the illness because of uncertainty as to the etiologic organism. Administration was as follows: 40 mg. intramuscularly every three hours and 40 mg. intrathecally daily for three days; 40 mg. intramuscularly every three hours for eleven days; 20 mg. intramuscularly every three hours for one day. The temperature became normal on the seventh day after starting streptomycin. On this day, five days after the last intrathecal injection of streptomycin, the spinal fluid streptomycin level was 2.5 micrograms per cc. and the plasma streptomycin level 10 micrograms per cc., three hours following injection of 40 mg. intramuscularly. During the period of intrathecal streptomycin administration the spinal fluid cell count increased from 1,370 to 3,800 per cu. mm., and the total protein from 80 to 175 mg. per 100 cc. Three days after the last intrathecal injection, the spinal fluid cell count was 800 per cu. mm.; the total protein had increased to 240 and the glucose from 15 to 32 mg. per 100 cc. Whether or not the intrathecal injection of streptomycin was irritating could not be determined clinically.

Recovery of the second patient (Case 21), a male age three, cannot be attributed solely to streptomycin since 6 Gm. of sulfadiazine daily were administered concurrently. In addition, anti-*Hemophilus influenzae* type b serum, 25 mg. of precipitable antibody nitrogen, were given on the second and 50 mg. on the fourth hospital day. However, in the opinion of the attending physician (Dr. Paul S. Rhoads) streptomycin was probably the more effective agent. *H. influenzae*, Type 3, was cultured from both spinal fluid and blood. The dosage of strepto-

mycin was 0.3 Gm. intramuscularly every three hours for nine days. During eight of these days 0.05 Gm. were injected intrathecally each day. Streptomycin levels of 6.25 and 3.125 micrograms per cc. were obtained twenty-four hours after two such intrathecal injections. The serum streptomycin level on these days ranged from 6.25 to 25 micrograms per c.c. The total dose of streptomycin was 22.4 Gm.

It has been demonstrated by Zintel et al.⁸ that in the normal subject streptomycin does not diffuse into the cerebrospinal fluid, but that in diseases of the meninges therapeutic levels may be reached after repeated parenteral injections. Our observations in Case 25 confirm this. In Case 21, streptomycin was administered intrathecally as well as intramuscularly because of the urgency to produce effective levels in the spinal fluid immediately.

There was no definite evidence that intrathecal injection of streptomycin is harmful.

BACTEREMIA

Herrell and Nichols² reported two cases of *Escherichia coli* septicemia which recovered following streptomycin therapy. In our case, as well as theirs, the septicemia was secondary to a urinary tract infection. (Fig. 1.)

The patient, a male, age forty-one, had a sudden onset of severe abdominal cramps and nausea. Pain later localized to the left side of the abdomen. Two days previously, gross, painless hematuria had occurred. On examination the patient complained of moderately severe pain in the left upper quadrant of the abdomen. Physical findings were normal except for tenderness in the left hypochondrium and pain on deep percussion over the left costovertebral angle. A tentative diagnosis of left renal colic was made. On admission to the hospital the temperature was 100°r., pulse 70, respiration 16. Urinalysis revealed a trace of albumin, 20 to 25 leukocytes and an occasional erythrocyte per high power field. The erythrocyte count was 4,390,000, hemoglobin 84 per cent. The leukocyte count was 10,800, with a differential of

69 per cent granulocytes and 31 per cent mononuclear cells.

On the second hospital day, the left kidney pelvis did not visualize on intravenous urography. An opacity, interpreted as a calculus, was seen in the region of the left ureter. Within

dropped to 2,050; the following day it had increased to 18,200.

On the fourth hospital day, streptomycin was begun in dosage of 0.5 Gm. intramuscularly every three hours. On this same day x-ray of the chest revealed bilateral basilar broncho-

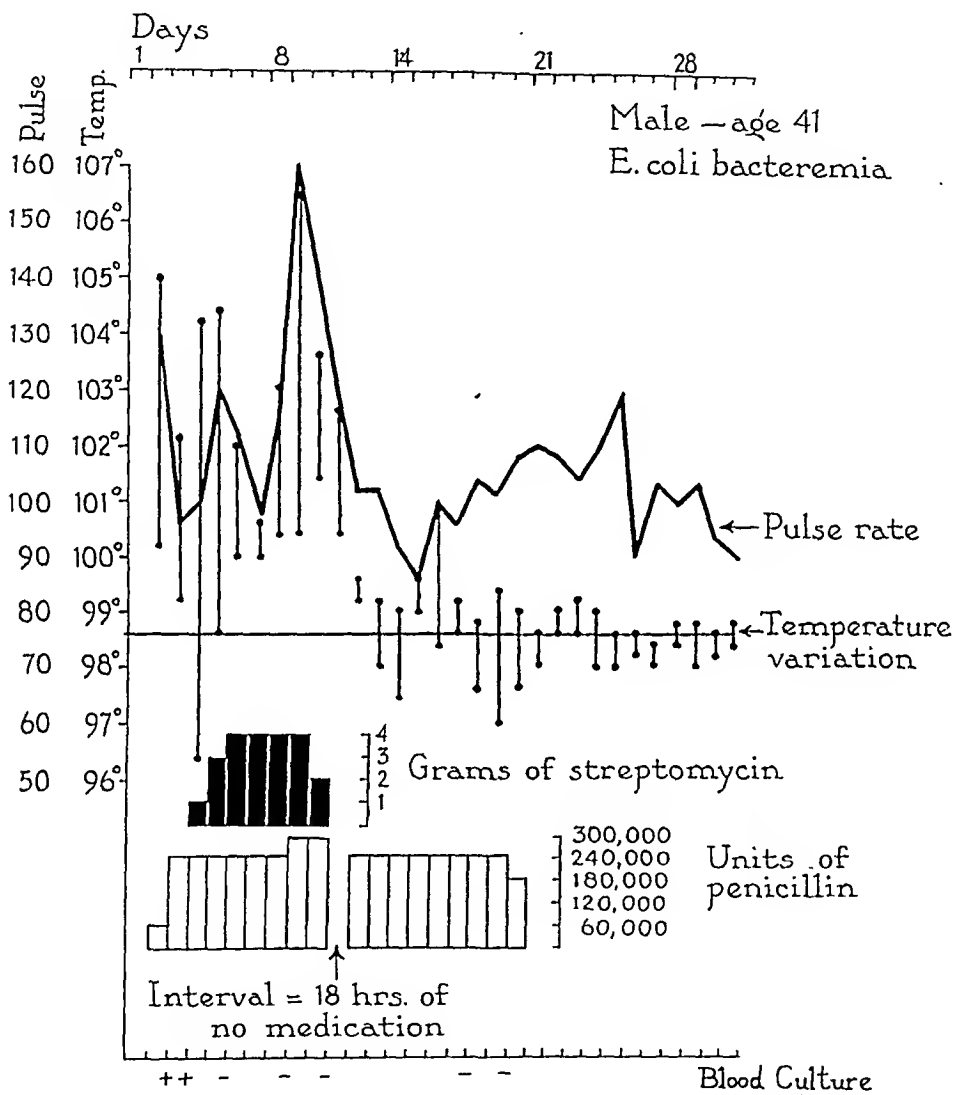


FIG. 1.

six hours after the pyelogram the patient had two chills followed by a maximum temperature of 105°F. The pulse was 130. Penicillin, 30,000 units intramuscularly every three hours, was started. Blood and urine cultures were positive for *Escherichia coli*.

A septic temperature with a maximum of 104.4°f. continued during the next three days. Sulfadiazine was given for twenty-four hours, but was discontinued when the leukocyte count

pneumonia. After two days of streptomycin therapy there was definite improvement. The maximum rectal temperature was 101.4°F., pulse 80, respiration 30. On the third day of streptomycin therapy and immediately following an injection, the patient developed a moderately severe attack of "asthma" and became very excited and apprehensive. Aminophyllin, 0.5 Gm., was given intravenously and the attack subsided within thirty minutes. Later, the pa-

tient again became very irritable, complained of headache and developed generalized muscular rigidity including rigidity of the neck. The deep tendon reflexes, however, were normal. Spinal fluid obtained by lumbar puncture was clear and under normal pressure. The cell count was 82 leukocytes and 7 erythrocytes per cu. mm. The total protein was 21 mg. per 100 cc. Culture was negative. Later in the day the patient developed a clonic convulsive seizure lasting over twenty minutes. This was relieved by sodium amytal, 0.5 Gm., intramuscularly. The right eye was deviated laterally during the seizure, and the rectal temperature rose to 106.6°F. Another convulsive seizure occurred the next day. Spinal fluid at this time contained 62 leukocytes per cu. mm. A diagnosis of toxic encephalopathy was made, and streptomycin and penicillin were discontinued. In the meantime the pneumonic symptoms had subsided. Following the peak of 106.6°F., the temperature began to fall, reached normal within seventy-two hours (fourteenth hospital day) and remained so. Repeated blood and urine cultures were negative. Two weeks later, another intravenous urogram revealed a normal left kidney, pelvis and ureter. A total of 18.1 Gm. of streptomycin was administered.*

In this case, the portal of entry was undoubtedly the left kidney. The cause of the toxic encephalopathy could not be determined with certainty. It might have been due to either streptomycin or penicillin since the cerebral symptoms subsided when both were discontinued. Penicillin therapy was later resumed, without producing further toxic reaction. Associated with one of the convulsive episodes was a temperature of 106.6°F. which subsided rapidly when penicillin and streptomycin were stopped.

* Since this paper was submitted for publication, this patient had several attacks of chills and fever which subsided under sulfonamide medication and streptomycin, either singly or in combination. Pyuria was not always present. Repeated cultures of blood were sterile. Intravenous and retrograde urograms were repeatedly not diagnostic. On March 1, 1947 the left kidney was explored and the upper pole found to be riddled with abscesses. The kidney was removed and to date the patient has remained well.

We have seen extreme hyperpyrexia in association with penicillin therapy.⁹ While chills and fever to 105° and 106°F. were frequently observed in the earlier days of penicillin therapy, convulsions and signs of toxic encephalopathy did not develop. Subsequently, as noted below, this patient received 1 Gm. of streptomycin per day without toxic reaction. It is unfortunate that both streptomycin and penicillin had to be used simultaneously in this case. It was deemed advisable to continue penicillin because of the bronchopneumonia. However, the therapeutic result as far as the septicemia is concerned must be credited to streptomycin because of the known insensitivity of *Escherichia coli* to penicillin, and because three days of penicillin therapy had been without effect on the septic process.

From June 1, to August 25, 1946, frequent cultures of urine revealed only *Monilia*. From 25 to 60 pus cells per high power field were constantly present. Intravenous urography on the latter date revealed a calculus in the left ureter at the ureterovesical junction. Meatotomy was performed and catheters inserted. Following this the temperature rose to 101°F. and culture of the urine showed *E. coli*. The fever did not subside and on the fourth day a severe chill occurred followed by temperature of 104°F. Repeated cultures of blood were negative. Streptomycin 1.0 Gm. per day was administered and the temperature promptly declined to normal and cultures of urine became negative. Apparently in this case there was no acquired resistance to streptomycin by the strain of *E. coli*.

CASE 24. A female, age fifty-three, developed a septic temperature with maximum of 103°F. two days following cholecystectomy, at which a subsiding acute cholecystitis was found. Surgery was difficult because of the inflammatory process and adhesions. Oozing was trouble-

some. Penicillin, 30,000 units intramuscularly, had been given from the first postoperative day. The dosage was increased to 100,000 units every three hours on the third postoperative day. Sulfadiazine, 5 Gm. per day, was added on the fourth, fifth and sixth postoperative days without affecting the septic course. On the sixth postoperative day the patient was acutely and severely ill; her temperature was 103°r., pulse 110, respirations 24. There was pain and tenderness in the right upper quadrant and over the liver. Blood culture was negative. A diagnosis of probable pylephlebitis was made. Penicillin and sulfadiazine were stopped and streptomycin 0.15 Gm., intramuscularly every three hours started. Improvement was prompt and rapid. The patient's temperature was normal seventy-two hours later and remained so.

While the diagnosis in this case may be open to question, the fact remains that a septic process developed following surgery in which the likelihood of invasion by coliform organisms was great, and that the sepsis developed and continued in spite of penicillin and sulfadiazine but subsided promptly following administration of streptomycin.

TOXIC REACTIONS

No serious toxic effects of streptomycin were noted in these twenty-six cases. Transitory vertigo was observed in two cases. Hinshaw and Feldman¹⁰ attribute this to a neurotoxic action on the eighth cranial nerve. Skin rashes were noted in two cases. In one, the rash was a diffuse erythema which disappeared without stopping streptomycin. In Case 2, urticarial wheals developed within a few minutes after starting an intravenous infusion containing 4.0 Gm. of streptomycin in 1,000 cc. of physiologic salt solution. Epinephrine (0.5 cc. of 1:1000 solution) afforded prompt relief. This patient had previously received 51.6 Gm. of streptomycin intramuscularly over a period of thirty-three days. The urticaria occurred upon resuming therapy after a lapse of

three days. When a new lot of streptomycin was received, intramuscular therapy was again resumed without recurrence of urticaria. This suggests that the reaction was caused by some impurity in a particular lot of streptomycin rather than by streptomycin itself. Most patients complained of pain at the site of injection. The discomfort varied considerably in severity, but usually subsided within an hour after injection. Headaches occurred occasionally but these could not be definitely attributed to streptomycin.

ABSORPTION AND EXCRETION

When streptomycin is administered parenterally, the main avenue of excretion is via the urinary tract. From 50 to 75 per cent of the drug can be recovered from the urine.¹¹ Serum and urine levels of streptomycin were determined on most of our patients. Following the initial intramuscular dose, blood was drawn in 60, 120 and 180 minutes, and at the same intervals after the corresponding dose on the following day. Assays were done according to the method of Heilman.¹² The average, maximal and minimal levels produced by intramuscular injection of 0.15 Gm. every three hours are recorded in Table II.

Urine levels were determined by the same method. The urine was collected 30, 90 and 150 minutes following the initial intramuscular dose and after the corresponding dose the following day. The average, maximal and minimal urine levels are recorded in Table III.

Other investigators^{8,11} have obtained blood levels up to 12 micrograms with repeated injections of 0.1 Gm. every three hours. It will be seen that our maximum blood levels with repeated injections of 0.15 Gm. every three hours are disproportionately higher although the mean level is about the same. Four patients receiving 0.3 Gm. every three hours had blood levels ranging from 3.125 to 80 micrograms per cc. Of fifteen

determinations, nine were from 12.5 to 25 micrograms per cc. Blood levels of 50 to 100 micrograms per cc. were repeatedly produced in one patient by 0.4 Gm. intramuscularly every three hours. This patient had moderate renal insufficiency. Our

TABLE II
BLOOD STREPTOMYCIN LEVELS (IN MICROGRAMS PER CC.)
OF 18 PATIENTS ON DOSAGE OF 0.15 GM.
INTRAMUSCULARLY EVERY THREE HOURS

Blood Sample	Average	High	Low
1 hour following initial dose	14.4	25.0	0.0
2 hours following initial dose	15.0	12.5	6.25
3 hours following initial dose	13.8	25.0	6.25
1 hour after corresponding dose next day	16.5	25.0	6.25
2 hours after corresponding dose next day	18.0	50.0	6.25
3 hours after corresponding dose next day	15.0	50.0	6.25

TABLE III
URINE STREPTOMYCIN LEVELS (IN MICROGRAMS PER CC.)
OF 18 PATIENTS ON DOSAGE OF 0.15 GM.
INTRAMUSCULARLY EVERY THREE HOURS

Urine Sample	Average	High	Low
½ hour following initial dose	80	400	25
1½ hours following initial dose	193	400	25
2½ hours following initial dose	280	800	50
½ hour after corresponding dose next day	375	1600	100
1½ hours after corresponding dose next day	350	800	50
2½ hours after corresponding dose next day	240	800	50

results confirm those of others that there is considerable individual variation in the blood streptomycin level resulting from the same dose, that an additive effect occurs with repeated injections and that abnormally high levels may be obtained in the presence of renal insufficiency.

SUMMARY

Nineteen cases of urinary infection due to gram-negative organisms were treated

with streptomycin. In sixteen of these the results were good. There have been no recurrences in the fourteen patients we have been able to follow over a period of one to six months. In two cases of acute brucellosis, streptomycin produced early subsidence of the symptoms and signs. No relapses have occurred in ten and five weeks, respectively. It is recognized that so short a time does not permit of a final conclusion. In one case of chronic brucellosis no demonstrable improvement occurred. One patient with *Hemophilus influenzae* meningitis was cured; in another case streptomycin was considered the most effective agent in producing recovery. Cure was effected in one case of septicemia due to *Escherichia coli*. One case of probable postoperative pyelophlebitis responded dramatically. No severe toxic effects were encountered. Blood and urine streptomycin levels obtained with various doses of streptomycin are reported.

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Clinical Studies in the Use of Myanesin*

EDWARD B. SCHLESINGER, M.D., A. LESLIE DREW, M.D. AND BARBARA WOOD, R.N.

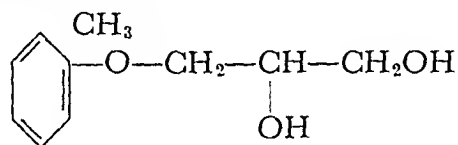
New York, New York

THE clinical applications of curare are based upon its ability to afford specific muscle relaxation. This property has led to increasing use of the drug as an adjuvant to anesthesia. Its value in ameliorating abnormal muscular mechanisms, i.e., muscle spasm, spasticity, rigidity and involuntary movement, is still under extensive clinical investigation.

It is commonly accepted that the chief action of curare in low concentration is at the myoneural junction. Autonomic and central synapses are affected significantly only at higher concentrations. Side effects are chiefly histaminic in type. At times these are of consequence in initiating abrupt falls in systolic blood pressure and, less frequently, in causing bronchospasm and laryngospasm. Less serious histaminic effects such as severe headache and urticarial reactions are of no concern to the anesthesiologist but they may interfere with treatment of neuromuscular disorders in the conscious patient.

The margin between adequate abdominal wall relaxation and respiratory failure due to curare paralysis of the muscles of respiration is not great. It is frequently necessary deliberately to invite this anesthesia complication in order to gain a satisfactory degree of relaxation. Under such conditions adequate respiratory exchange is maintained by manual compression of the gas bag until function is restored. The relative ease of reversibility of pharmacologic effects and freedom from pronounced side reactions in other organ systems has endeared the drug to many anesthesiologists. Nevertheless, curare is by no means the ultimate drug of choice either in anesthesia practice or in the

treatment of neuromuscular disorders. Its proven value, however, has stimulated wide interest in drugs of like pharmacologic properties. This report represents a clinical evaluation, particularly in the treatment of abnormal neuromuscular mechanisms, of one such drug, myanesin, (α,β -dihydroxy [2-methyl phenoxy]-propane):*



Interest in this drug followed upon the reports of the British pharmacologists, F. M. Berger and W. Bradley^{1,2} and the clinical investigations of F. B. Mallison,³ an anesthesiologist. Although it has been known since 1909^{4,5} that the alpha-ethers of glycerol are capable of producing paralysis, no real interest in the subject developed prior to the reports of these later investigators.

The manner in which this series of drugs came under investigation is of interest.† Dr. Berger was asked to study the pharmacologic side effects of phenoxetol which at the time was being used as a preservative for penicillin in England. He discovered that this drug had effects similar to myanesin but of a lower order. Interest being aroused, further investigations were carried out during which myanesin proved to be the most satisfactory compound tested.

Pharmacologic Data. The clinical product, myanesin, is a colorless, crystalline solid, melting at 70 to 71°C. Its solubility at 22°C. is 1.09 Gm. per 100 cc., but strong, stable,

* Supplied through the courtesy of E. R. Squibb & Sons and Abbott Laboratories.

† Personal communication.

* From the Department of Neurology, College of Physicians and Surgeons, Columbia University, the Neurological Institute of New York and the Institute for Crippled and Disabled. These studies were aided by a grant from the National Foundation for Infantile Paralysis.

saturated solutions can be obtained by preparing solutions at higher temperatures and allowing them to cool. Higher concentrations necessitate the use of solubilizing agents. Among those which have been used are alcohol, propylene glycol and urea and its derivatives. With alcohol and propylene glycol a stable 10 per cent solution has been prepared which is in use in Great Britain. Solutions can be sterilized by heating and are miscible with sodium chloride, glucose and barbiturate (including thiobarbituric acid) preparations.

Previous reports are based on the use of 10 per cent myanesin in propylene glycol and alcohol. A 2 per cent solution of myanesin in normal saline was prepared in our laboratory which was stable and proved clinically effective. This preparation was used throughout this study. The adjuvants necessary to maintain solution at 10 per cent concentration obviously interfere with study of pure drug effects. In addition, there is a significantly high incidence of phlebitis following their use. Another grave contraindication lies in the production of hemolysis and hemoglobinuria⁶ by higher concentrations of myanesin and solubilizing agents. The disadvantage of a 2 per cent solution lies in its bulk. Although this seems to have been considered a serious drawback to its clinical introduction in England, it has seemed to us of minor importance.

USE OF MYANESIN IN AMELIORATION OF NEUROMUSCULAR DISORDERS

Technical Data. Myanesin is so rapidly metabolized that an effective concentration, once achieved, must be maintained by constant injection of the drug since there is no significant cumulative or residual effect. The exact mode of breakdown, or the organ system involved, is not known. Urine specimens contain only small quantities of active substance even when high concentrations have been given intravenously.⁷ The duration of action is brief and, without exception, is terminated within five hours after injection. The effect is usually extremely short lived and may disappear as

soon as the infusion is stopped. This fact limits the therapeutic value of the drug. Other routes of injection are not feasible at present. To obtain a clinical response by oral administration, huge doses are necessary and even these have only an ephemeral and inconstant effect.

Technic of Administration. Depending upon the rate of injection, 50 to 150 cc. of 2 per cent myanesin given intravenously will afford excellent reduction of certain abnormal neuromuscular mechanisms in the adult human being. The speed and degree of effect is greatly dependent upon the rate of injection and the nature of the disease treated. In clinical use the following method has been adopted: A 2 per cent solution of the drug is started into an antecubital vein at the rate of 30 drops per minute. After one minute, if no unusual effect is seen and no subjective reactions have been reported, the rate is increased to 40 drops per minute until a therapeutic effect is obtained or certain side reactions are noted. As soon as the desired result is obtained the drip rate is readjusted to maintain an effective level without superimposition of side reactions. The patient is tested prior to injection for the presence of horizontal and vertical nystagmus. This testing continues during injection of the drug. As an effective level is approached one notes an increase in the amplitude and ease of elicitation of horizontal nystagmus. Rotary and then true vertical nystagmus appear. This roughly coincides with desired therapeutic levels in most cases and is, therefore, a useful clinical sign.

CLINICAL OBSERVATIONS DURING ADMINISTRATION OF MYANESIN

Since this drug was so recently introduced and its effect therefore still poorly understood, it may be worth while to describe the events seen in a large group of patients during the administration of increasing amounts. As previously mentioned, horizontal, rotary and vertical nystagmus are almost constantly seen as the concentration rises. At the same time, the patient may

complain of blurring of vision, probably due to extra-ocular muscle imbalance. Almost immediately, patients describe a feeling of warmth and very often of circumoral numbness, or "pins and needle" sensation. This circumoral distribution seems to correspond with the circumoral onion peel area of Dejerine-Kraus-Schlesinger. Dryness of the mouth may be noted concomitantly. There is a drop in systolic blood pressure averaging 30 mm. Hg at the same time as the subjective feeling of warmth. At this point injection of the cornea is also noted. The patient now usually describes a pleasurable feeling of relaxation and drowsiness. If injection is pushed rapidly at this juncture, the subject may go on to what appears to be natural sleep from which he can be easily aroused. Many patients during the initial injection phase become euphoric, talkative and show relaxation of nervous tension. If the patient is carefully tested at this stage, a mild degree of incoordination may be seen although no true muscle weakness is present. A small group of patients consistently note nausea; this is most pronounced when the drug is administered orally. If the drug is rapidly administered while the patient is showing the aforementioned effects, he may go through a period of increased reflexes and what appears to be decerebrate rigidity. Decerebrate rigidity has been consistently seen in animals at high drug concentration. This has been considered to be a stimulant effect of the drug but probably represents a release phenomenon based on high brain stem depression.

The pharmacology and chemistry of myanesin have not been explored sufficiently to make dogmatic statements as to the exact site and mechanism of its action. It is safe to state, however, that the drug is a spinal cord and brain stem depressant and that its effects on cortical synapses are dependent upon much higher concentrations. Although it has been shown to have some peripheral neuromuscular effect, this is not of the order of magnitude of its spinal cord depressant action. The amelioration of

abnormal innervation cannot be attributed to a curare-like myoneural junction effect. Of great interest is the fact that myanesin is an efficient local anesthetic comparable to procaine. Corneal anesthesia can be obtained with surface application of the drug,

TABLE I
CASE ANALYSIS

Mechanisms Treated	No of Cases
Muscle spasm	25
Spasticity (abnormal stretch response)	30
Mass reflexes	16
Rigidity	8
Tremor	12
Involuntary movement (athetosis, dystonia)	10
Muscle splinting (acute anterior poliomyelitis)	2
Catatonia	2
Pain	
Neuritic	5
Causalgic	3
Convulsive movement (induced electric shock)	10

but when given by injection it has a definite irritant effect.

In therapeutic concentrations the chronic toxicity of myanesin is of a low order and no deleterious effects on any organ system have been noted after repeated injections. However, there is great potential danger in the use of the drug in that high concentrations or effective concentrations introduced too rapidly may lead to cardiac arrest following depression of sino-auricular node activity. Actually, the margin between cardiac effects and clinically efficient doses is very wide. The margin between good surgical relaxation and diaphragmatic paralysis is appreciably greater with myanesin than with curare. It is, therefore, obvious that the drug will be widely studied as a substitute for curare in surgical anesthesia. Since this is not the subject of the present report, it is discussed only in passing.

Clinical Data. The rapid disappearance of clinical effects together with limitations in the routes of administration unfortunately narrow the use of myanesin as an agent in ameliorating abnormal neuromuscular mechanisms. With the above facts in mind, administration of the drug was limited to the following types of cases: (1) True muscle spasm, (a) the acute low back; (2) spasticity,

(a) cord injury, (b) cerebral palsy, (c) cortical injuries; (3) rigidity, (a) parkinsonism; (4) tremor, (a) parkinsonism; (5) involuntary movement, (a) dystonia, (b) athetosis, (c) heterogeneous dyskinesias; (6) miscellaneous entities, (a) acute anterior poliomyelitis, associated with limitation of range of motion of the back and extremities, with pain on such motion, (b) pain associated with nerve root compression where muscle spasm seems to be a secondary protective splinting device. Such muscle spasm is usually not completely reversible except as a result of relief of the original lesion, (c) Marie-Strümpell arthritis. (Table I.)

RESULTS

Muscle Spasm. The use of curare as a specific muscle relaxant has been applied to the treatment of acute muscle spasm of so-called "acute low-back."⁹ When the disorder is not chronic and deep seated, curare has proved to be a very useful agent in reducing the muscle spasm, thereby breaking up what appears to be a vicious cycle of pain and muscle splinting. Aqueous solutions of curare are not employed for this purpose for obvious reasons, but with long-acting suspensions of curare in oil and wax a worth while result may be achieved in properly selected patients. With intravenous myanesin, relief of the acute muscle spasm occurs almost instantly, that is, within the few seconds necessary to obtain a therapeutic concentration intravenously. This dissolution of muscle spasm is abrupt, dramatic and can be obtained with concentrations which are completely safe and not characterized by muscle weakness. When the lesion is reversible, as in the "acute low-back," the desired therapeutic effect is perpetuated once good relaxation occurs. It is impossible to state with certainty that the analgesic effect of the drug does not contribute to this dramatic therapeutic effect. Nevertheless, it is sufficiently striking to be of great clinical interest.

Spasticity. It was apparent after preliminary experiments that the evanescent

effect of the drug would markedly limit its usefulness in the treatment of chronic disabilities such as spasticity. The following uses were considered: (1) to evaluate the reversibility of contractures and deformities. Very often in a given patient it is impossible to state at the onset of treatment that loss of range of motion is completely reversible or partially based on fibrosis, contracture or joint changes; (2) theoretically, to afford an opportunity to reduce or prevent contractures by competent physical therapy given while the subject is under the influence of repeated injections of the drug.

In spasticity, it is possible to reduce the hyperactive stretch reflex to normal and accordingly gain complete range of motion without eliciting abnormal contractions. This reduction in spasticity is not accompanied at efficient levels by motor weakness. However, the desired effect is rapidly dissipated and on no occasion has lasted more than forty-five minutes after cessation of injection.

These conclusions do not parallel those of Stephen and Chandy.⁸ These investigators believed that myanesin had no effect upon spasticity following spinal cord lesions. Our experiences with spastic paraplegia following cord severance suggest that myanesin has pronounced depressant effects upon the isolated or partly isolated spinal cord.

During administration of the drug there is a marked change in reflex phenomena in the involved extremities. During the phase of muscle relaxation clonus may be brought out more easily because of the reduction in pipe-stem tension in the muscles. Depending upon the concentration of the drug in the blood stream, there may later appear increased reflex activity with new so-called pyramidal tract signs or the desired depression of abnormal reflexes. The variation in reflex status depends upon the degree of long tract depression by myanesin at the brain stem and cord levels versus local cord and brain stem depression. These findings are not in keeping with the observations of Stephen and Chandy.⁸ These investigators, however, performed all

their experiments with a 10 per cent solution of myanesin in propylene glycol and alcohol. The variation in concentration of myanesin and the introduction of two pharmacologically potent solubilizing agents may account for the difference in results.

Rigidity. Rigidity, in general, responds less favorably than tremor to the drugs which are presently in vogue. It was considered of great interest to determine the effect of myanesin upon this entity. Curare had previously been shown¹⁰ to afford no more than a modicum of reduction in the abnormal muscle tension although it occasionally was of therapeutic advantage. In patients with rigidity there appeared to be an unusual sensitivity to myanesin. It was possible routinely to release the rigidity almost completely and in effect restore the motor apparatus to normal for the duration of drug effect. Interestingly enough, the duration of effect was longer in these patients than in any other type of lesion treated, persisting up to five and one half hours. It was also possible to elicit side effects much more rapidly in lower concentrations than with any other disease entity.

Tremor. Along with rigidity it was possible to influence tremor rapidly and with small concentrations of drug. The tremor persisted longer than the rigidity and at times the tremor could be brought out by active exercise after it had disappeared at rest. In certain subjects the tremor disappeared completely for approximately the same length of time as the rigidity. In other individuals a certain suggestion of decomposition of movement persisted; or it was necessary to produce mild weakness in order to maintain absence of tremor.

Involuntary Movement. Involuntary movement responded rapidly and at safe therapeutic levels. As with tremor, there was at times a residual coarse representation of the pathologic mechanism present even though the major dyskinetic phenomena had disappeared. Again, as with tremor, the drug had to be pushed at times to a point where certain side effects occurred which inter-

fered with patient function. In general, the immediate effect was spectacular but not prolonged beyond forty-five minutes after the presence of therapeutic levels in the blood stream.

Myanesin appears to be useful also in the treatment of athetoid crisis. A patient suffering from an acute athetoid crisis was kept completely free of motor activity throughout the administration of the drug and for forty-five minutes thereafter. The effect was at least as efficient as hypnotic doses of barbiturates and had the advantage of permitting the attending physician to deal with a conscious patient in full command of his protective reflexes.

Miscellaneous Entities. (a) During the acute stage of anterior poliomyelitis marked reduction in mobility of the truncal muscles and in range of motion of the extremities frequently occurs. Motion of the extremities is associated with extreme pain. It is felt by some clinicians that this immobility may lead to permanent deformities. Accordingly, a great deal of attention is directed against the so-called "muscle spasm" of poliomyelitis. It is not the purpose of this paper to discuss the physiologic mechanisms which underlie so-called "muscle spasm." The authors believed that by the use of a drug such as myanesin a great deal might be learned about the nature of this entity. Accordingly, subjects were chosen who exhibited frank reduction in range of motion of the lower extremities. Previous examinations had been recorded and the range of motion tested by staff therapists. The patients were then given myanesin to therapeutic levels and again tested by the same observers. At this point the muscles were noted to be relaxed to such a degree that it would be facetious to speak of "muscle spasm." The patients' demonstrable range of motion, nevertheless, was little if any increased in spite of flaccidity in the muscles. It was the impression of the experimenters that pain appeared, just as previously, at a point where there was stretching of the spinal elements: roots, root sheaths, spinal ganglia and meninges. These

observations support the view that "muscle spasm" represents protective splinting of involved spinal elements rather than true contractures of striated muscles as a primary event.

(b) In patients in whom there was true root compression, such as with herniation of the nucleus pulposus, interesting observations were made. Surprisingly, it was frequently possible to relieve completely the pain and deformities coexisting with these lesions. However, the pain invariably returned rapidly. The shortest duration of complete relief was three and one half minutes and the longest eighteen hours. These results must be interpreted as due to relief of pain by relaxation of muscle and possibly, therefore, to reduction of pressure by skeletal elements on nerve roots. On the other hand, the relief may in part be based on the analgesic effect of the drug. Preliminary investigation reveals that in states characterized by primary pain, such as neuritis, no such effect was noted.

In several patients with dislocation or partial dislocation of vertebrae pain was relieved for the duration of injection of the drug and, at times, for several hours thereafter. The usefulness of the drug in assisting reduction of such dislocations has been incompletely explored as yet. In the foregoing entities, referred pain was always dissipated almost immediately. This may prove to be useful in evaluating the underlying pathologic condition and myanesin may therefore be an important agent in the study of such lesions as the frozen shoulder, cervical disc and shoulder-hand syndrome.

(c) The exact pathologic mechanisms underlying the pain and immobility of acute Marie-Strümpell arthritis are poorly understood. Pain is excruciating at times and the accompanying muscle spasm severely limits range of motion. The prolonged loss of range of motion possibly exerts a deleterious effect on muscle length, blood supply and the possibility of restoration of normal skeletal mechanics. Since the pathogenesis of the disease is obscure, it was believed to be of interest to try myanesin in acute

Marie-Strümpell arthritis. It was reasoned that if the pain were due to extreme muscle splinting or spasm rather than to an inflammatory or neuritic phenomenon, it might be resolved by muscle relaxation. Diagnosis in the first patient chosen was verified by three competent observers. Pain could not be controlled by traditional means and at the time the patient was first seen the act of moving from a bed to a stretcher was too excruciating to be borne. The patient was given intravenous myanesin and within thirty seconds after vertical nystagmus had appeared he was completely free of pain and could flex and extend his extremities and his truncal muscles freely. The intravenous injection was discontinued after the injection of 150 cc. of the drug and the patient was allowed out of bed. At this time his range of motion was normal and could be carried out without pain. Further treatment of this patient consisted in maintenance of some degree of muscle relaxation with curare in oil and wax. Continuous progress in such patients is of interest since long-term follow-up examinations should reveal the presence or lack of development of typical vertebral changes. If these latter do not appear, their pathogenesis may in part be blamed upon the early acute muscle spasm and accompanying loss of range of motion. The acute experiment described, however, suggests only that pain is based on muscle spasm rather than on inflammatory neuritis or compression of nerve roots.

GENERAL OBSERVATIONS

In a large series of subjects 2 per cent myanesin was used with a wide margin of safety. No respiratory depression was noted, no cardiac effects, no dramatic drop in systolic blood pressure and no significant changes in vital signs. At no time was hemoglobinuria induced even after repeated injections. Likewise, phlebitis did not occur although the same vessels were repeatedly used. Electrocardiograms at therapeutic drug levels showed no deviation from the previous pattern and no changes in cardiac

function were demonstrated on examination. Although myanesin in large doses is capable of depression of cortical potentials, test subjects showed no electroencephalographic changes at the time they exhibited maximal relief of their clinical syndrome.

On the other hand, incoordination, lassitude and blurring of vision very often restricted the possibility of getting a patient out of bed after administration of the drug. By the time all of these signs had disappeared the desired clinical effect usually was lost.

COMMENTS

The properties of myanesin place it in an unusual pharmacologic niche. Although its chief sites of action seem to lie in the spinal cord and brain stem, it has many other properties. At certain concentrations it has definite hypnotic effect, at others it is an effective local anesthetic. Its curare-like action seems of minor import but its ability to depress cortical potentials relates it more closely to the barbiturates. Its efficiency in ameliorating involuntary movement, rigidity, spasticity and tremor are of a higher order than that of the curare series, and at least comparable to any known therapeutic agent. Its site of action in the brain stem possibly contributes to its unusual efficiency in these disorders. Unfortunately, the evanescent nature of its effects makes it more of a laboratory tool than a therapeutic agent, except in certain specific instances. Toxic manifestations have been fairly well outlined. At high concentrations the drug has a quinidine-like action, prolongs the refractory period of cardiac muscle and may critically depress sino-auricular node activity and lead to ventricular standstill. These cardiotoxic concentrations lie outside the realm of therapeutic needs and the margin of safety is comfortably wide. The production of hemolysis limits the use of high concentrations of the drug. Solubilizing agents are necessary to maintain such concentrations and these are undesirable. In 2 per cent solutions neither hemolysis nor phlebitis has been a problem. At present the

use of myanesin seems limited to the intravenous route of administration. Oral administration yields completely unpredictable results with inefficient therapeutic effects at best. Oral administration seems to cause a greater incidence of nausea than any other route of administration. Intramuscular injection of myanesin in concentrations higher than 2 per cent leads to necrosis and evidence of severe inflammatory reaction in the tissues. These changes do not occur when a 2 per cent solution is used. The bulk necessary for effective doses of 2 per cent solution by the intramuscular route makes such a technic of administration unfeasible. Chronic changes incident to prolonged use of the drug have not been noted as yet and there is no demonstrable toxic effect on any organ system incident to such use. The exact mechanism of breakdown of the drug in the body is not understood. Unlike curare, it is almost completely metabolized and little is put out in the urine intact.

Myanesin is a simple drug to synthesize and one which entails no great expense in manufacture. A great many analogues have been studied but as yet none of this series of drugs has shown any positive advantage over myanesin.

One of the great drawbacks to the proper evaluation of curare lies in the difficulty of ascertaining blood concentrations. Efficient methods of determining myanesin blood levels^{7,11} have already been described.

The use of myanesin clinically for treatment of reversible muscle pathologic disease such as muscle spasm seems practical and efficacious. Its value as an aid in manipulation of painful contractures and dislocations deserves further investigation. It should prove of great worth in the proper evaluation of muscle deformity and contractures.

In effective therapeutic concentrations few of the known toxic effects have been seen. Certain entities have proven more sensitive to the drug and in these there has been more rapid appearance of side effects. This has been particularly true in parkinsonism and less markedly so in athetosis. The residual effects in parkinsonism were

maintained for a longer period than in any other condition treated. It is the authors' opinion that this drug will not replace curare in the treatment of spasticity and rigidity since prolonged duration of effect cannot be maintained. Its usefulness in anesthesia was not sufficiently explored in this study to venture any opinion as to its effectiveness in that sphere. However, the degree of synergism between myanesin and the barbiturates is striking and undoubtedly will increase the value of the drug as an adjuvant to intravenous pentothal anesthesia.

CONCLUSIONS

1. Myanesin in 2 per cent solution is capable of affecting the abnormal neuromuscular mechanisms underlying muscle spasm, spasticity, rigidity, tremor and the dyskinesias.

2. The primary site of action of this drug appears to be the brain stem and spinal cord.

3. In addition to its spinal cord and brain stem depressant action, the drug has local anesthetic activity of the order of procaine and in certain concentrations has a hypnotic effect of the order of the barbiturates.

Although it is known that myanesin has a curare-like action peripherally, this is of a low order and is not responsible for the major pharmacologic effects of the drug.

4. The margin of safety with 2 per cent solutions seems sufficiently wide to make the drug of therapeutic value.

5. At such concentrations, neither hemoglobinuria nor phlebitis was produced.

6. During administration of 2 per cent myanesin in the human subject the following side-effects have been regularly noted: (a) horizontal nystagmus, (b) a feeling of warmth, (c) circumoral numbness or "pins and needles" sensation, (d) a mild fall in systolic blood pressure, (e) corneal injection, (f) vertical nystagmus, (g) blurred vision, (h) dry mouth, (i) euphoria, (j) slight general muscular incoordination and (k) drowsiness.

7. Myanesin is worthy of further trial as a therapeutic agent in the treatment of true muscle spasm.

8. In the treatment of other neuromuscular entities myanesin seems of great academic interest but of limited clinical value.

9. The neural mechanisms underlying parkinsonism seem to be particularly sensitive to the action of the drug.

10. The use of myanesin in eliciting basic mechanisms underlying the changes of acute poliomyelitis and Marie-Strümpell arthritis is described.

11. Myanesin is suggested as a useful agent in evaluating the nature of muscle contractures and deformities in a wide variety of conditions.

12. Further studies of its pharmacologic effects are necessary.

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Correlation between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma^{*}

RENÉ WÉGRIA, M.D. and MARGARET N. BOYLE, M.D.

New York, New York

IN recent years, the importance of the relationship between the concentration of a drug in the blood and the intensity of its effect has been recognized and many such correlation studies have been made. Most of these studies, however, have been devoted to the action of drugs like the sulfonamides and penicillin, whose main site of action is probably the blood and body fluids. When a drug is used for its effect upon tissue cells, for example quinidine for its effect on the heart, the problem becomes more complicated. Obviously, in trying to understand fully the quantitative aspect of the effect of such a drug, the first problem is to establish the relationship between the concentration of the drug in the heart muscle and the intensity of the effect the drug has on the heart. The second step is to establish the relationship between the concentration of the drug in the blood and its concentration in the heart muscle.

To determine the relationship between the blood and tissue concentration of a drug and the effect it has on an organ, it is necessary to have a method of determining the concentration of the drug in the blood and in the organ and also a method of quantitating the effect that the drug has on the organ. Methods of estimating quinidine in the blood and tissues are now available¹ and the measure of the variations of the rate of the circus movement in auricular fibrillation offers a method of quantitating the effect quinidine has on the heart or at least on the auricles.² As permanent auricular fibrilla-

tion cannot be reproduced in animals, it is impossible to use animal experimentation in order to correlate the concentration of quinidine in the blood, the concentration of quinidine in the atrial muscle and the effect of quinidine on the circus movement of the fibrillating auricles. Furthermore, since it is not feasible to determine the concentration of quinidine in the auricular tissue of patients, the only approach is to study in patients with chronic auricular fibrillation the correlation between the effect of quinidine on the rate of the circus movement and the concentration of quinidine in the blood.

It is the purpose of this paper to report, in the first part, observations made on patients of the relationship between the concentration of quinidine in the blood plasma and the intensity of the effect of the drug upon the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. In the second part are reported the results of studies made on dogs in an attempt to correlate the concentration of quinidine in the blood plasma and its concentration in several tissues including atria and ventricles.

STUDIES MADE ON HUMAN SUBJECTS

Methods. The concentration of quinidine base in the blood plasma and in tissues was determined by the method of Brodie, Udenfriend, Dill and Downing.¹ The rate of the circus movement in the auricles was determined by the method first suggested by Lewis.² Two non-polarizable electrodes

^{*}From The Department of Medicine, Columbia University, College of Physicians and Surgeons and the Presbyterian Hospital, New York, N. Y. Supported by a grant from the Life Insurance Medical Research Fund.

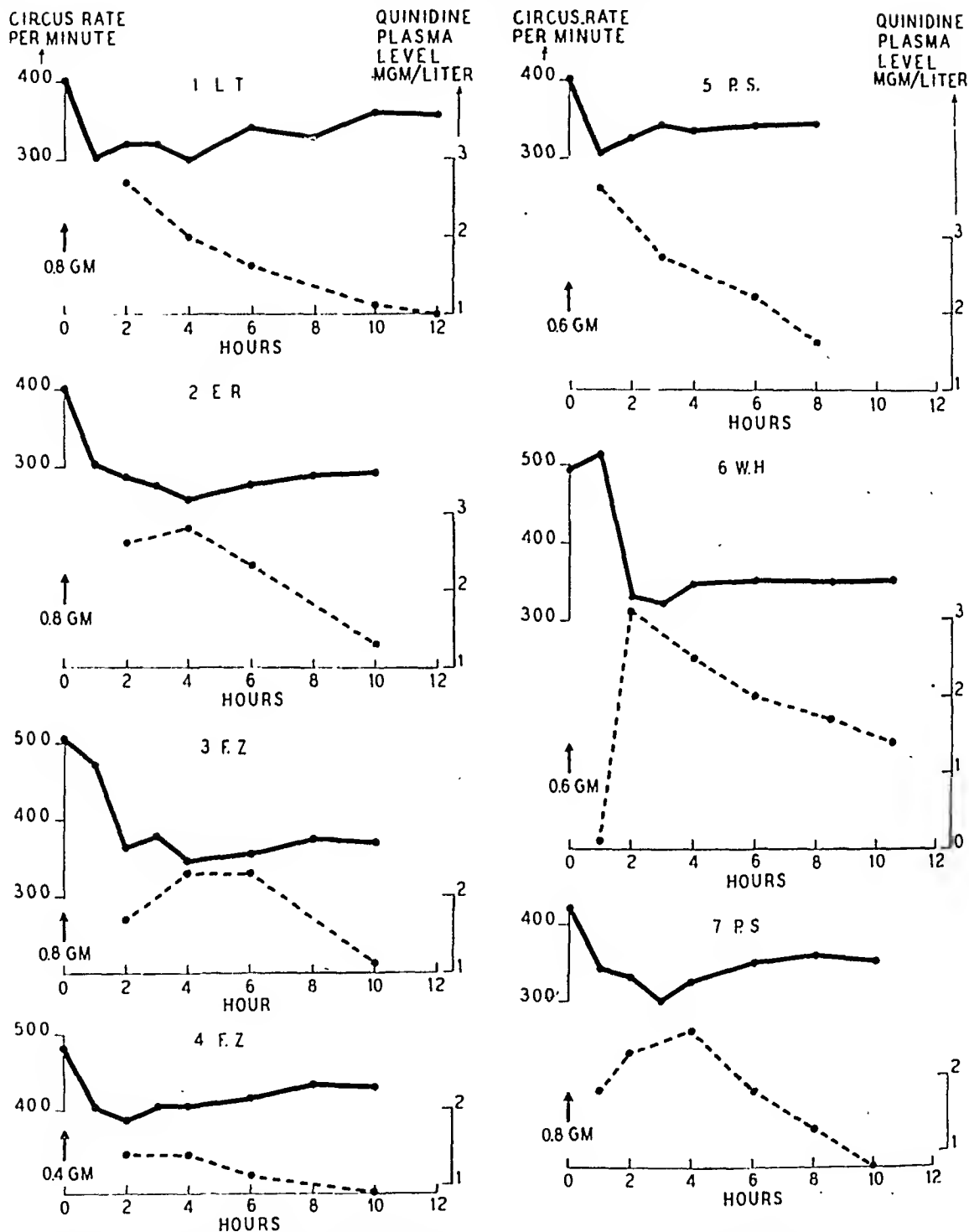


FIG. 1. Correlation between the quinidine plasma level and the effect of quinidine on the rate per minute of the circus movement in chronic auricular fibrillation in seven studies on five patients. In each study the upper curve is the rate of the circus movement per minute, the lower curve the quinidine plasma level expressed in mg. of the base per liter. Time in hours. The arrow in each experiment indicates the time at which quinidine sulfate was administered orally and the figure under each arrow is the dose of quinidine sulfate given.

were placed on the chest along the right sternal border and connected to the electrocardiograph. Their optimal location varied slightly in different patients. Having once determined in a given patient the points at

due to auricular activity were obtained in the precordial derivation used. Unfortunately, relatively few such patients are available as auricular fibrillation of such a type is uncommon in chronic auricular fibrilla-

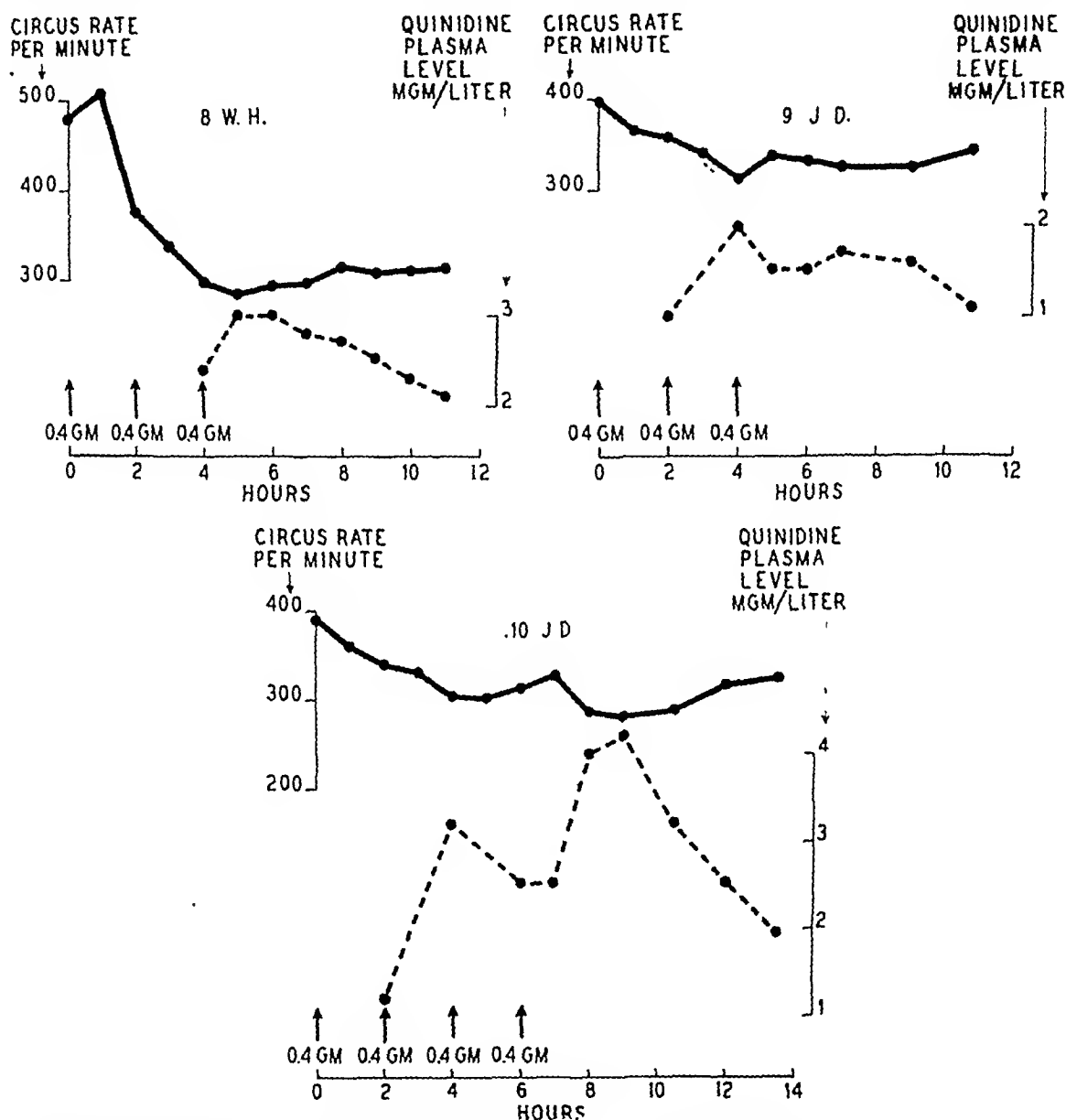


FIG. 2. Correlation between the quinidine plasma level and the effect of quinidine on the rate per minute of the circus movement in chronic auricular fibrillation in three studies on two patients. In each experiment the upper curve is the rate of the circus movement per minute, the lower curve the quinidine plasma level expressed in mg. of the base per liter. Time in hours. The arrow in each experiment indicates the time at which quinidine sulfate was administered orally and the figure under each arrow is the dose of quinidine sulfate given at the arrow.

which maximal deflections of auricular origin were obtained, the location of the electrodes was kept constant. Patients were selected in whom the auricular fibrillation was of a coarse type so that good deflections

tion. It is most common in paroxysmal auricular fibrillation and auricular fibrillation of recent onset but such patients in the course of quinidine therapy, even with small doses, frequently revert to regular sinus

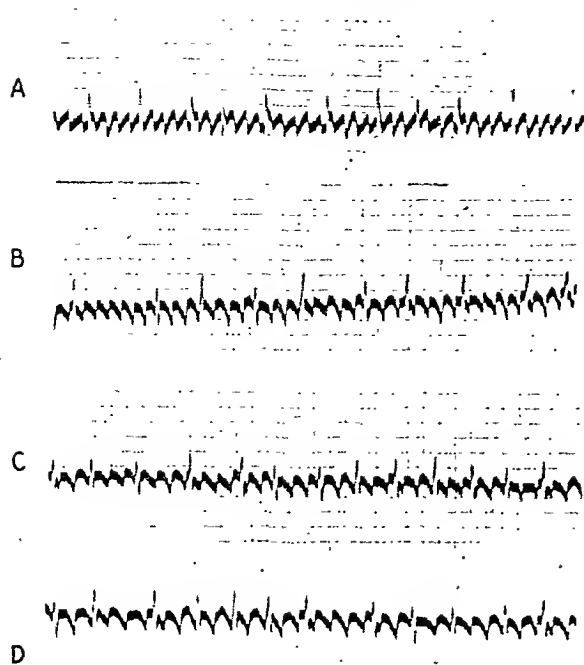


FIG. 3. Chest leads of study 10. The patient received 0.4 Gm. quinidine sulfate at 9 A.M., 11 A.M., 1 P.M., and 3 P.M. A, control record taken at 9 A.M.; circus rate 391 per minute. B, record taken at 11 A.M.; circus rate 340 per minute. C, record taken at 1 P.M.; circus rate 305 per minute. D, record taken at 5 P.M.; circus rate 287 per minute.

rhythm, thus terminating the study prematurely. The patients were fully digitalized at least two weeks before the administration of quinidine, placed on a maintenance dose of digitalis at least one week before the study was begun and were kept on a maintenance dose of digitalis throughout the quinidine study. Each patient received a test dose of 0.2 Gm. quinidine sulfate a few days before the study was begun to screen out patients with idiosyncrasy to the drug. The patients were kept in bed during the observations. A control electrocardiogram was taken the day before the quinidine study. The day of the study, after a control electrocardiogram was taken, the patient was immediately given the dose or the first of repeated doses of the drug; then electrocardiograms and blood samples were taken at various intervals. When repeated doses were given, each additional dose was administered immediately after an electrocardiogram and a blood sample had been taken. When the

same patient was used more than once, a period of at least eight days was always allowed to elapse between periods of study.

Results and Discussion. Ten studies were made on six patients. In the first seven studies made on five patients (L. T., E. R., F. Z., P. S., W. H.), a single dose of quinidine sulfate was given. (Fig. 1.) In the last three studies performed on two patients (W. H., J. D.), repeated doses of quinidine sulfate were given, 0.4 Gm. every two hours for three doses in two studies and 0.4 Gm. every two hours for four doses in the last study. (Fig. 2.) Figure 3 shows electrocardiographic tracings obtained in the tenth study before and after the administration of quinidine.

In analyzing the results obtained after the oral administration of a single dose (Fig. 1), it is obvious from the curves representing the rate per minute of the circus movement and the plasma quinidine concentration that the effect on the circus rate is roughly parallel to the plasma quinidine concentration. For example, the maximal cardiac effect is obtained within four hours and the maximal quinidine level is also reached within four hours. This parallelism between quinidine plasma concentration and cardiac effect of the drug has also been observed recently by Linenthal, Ulick and Patterson³ and by Delevett and Poindexter.⁴ However, if our results are scrutinized more closely, it is apparent that there is no strict quantitative relationship between the cardiac effect and the plasma concentration of quinidine. In the second study, for example, two hours after the oral administration of 0.8 Gm. of quinidine sulfate, the circus rate fell from 402 to 285 per minute and the plasma concentration of quinidine was 2.6 mg. per liter, whereas ten hours after the administration of quinidine, the circus rate was practically the same, 292 per minute, but the plasma concentration of quinidine was only 1.3 mg. per liter, i.e., much lower than two hours after the administration of the drug. In the third study, the circus rate was the same, i.e., 364 and 371 per minute, two hours and ten hours respectively, after

the oral administration of 0.8 Gm. of quinidine sulfate but the plasma concentration was 1.7 mg. per liter two hours after the administration of the drug and only 1.1 mg.

TABLE I*

Study No.		Circus Rate Per Minute	Quinidine Plasma Level in Mg. Per Liter
2	Control	402	
	2 hours after administration of 0.8 Gm. quinidine sulfate	285	2.6
	10 hours after administration of 0.8 Gm. quinidine sulfate	292	1.3
3	Control	505	
	2 hours after administration of 0.8 Gm. quinidine sulfate	364	1.7
	10 hours after administration of 0.8 Gm. quinidine sulfate	371	1.1
5	Control	401	
	3 hours after administration of 0.6 Gm. quinidine sulfate	342	2.7
	8 hours after administration of 0.6 Gm. quinidine sulfate	346	1.6
6	Control	497	
	4 hours after administration of 0.6 Gm. quinidine sulfate	345	2.5
	10 ½ hours after administration of 0.6 Gm. quinidine sulfate	351	1.4
7	Control	422	
	1 hour after administration of 0.8 Gm. quinidine sulfate	342	1.8
	10 hours after administration of 0.8 Gm. quinidine sulfate	352	0.8

* Table summarizing the main discrepancies between quinidine plasma level and intensity of the cardiac effect observed in studies of Figure 1.

per liter ten hours after the administration of the drug. The fifth, sixth and seventh studies also show similar discrepancies. (Table I.)

In the eighth, ninth and tenth studies (Fig. 2) repeated doses of quinidine were given. The reasons for making these studies were that quinidine sulfate is usually administered to patients in repeated doses and also that it was hoped that such experiments might help in understanding the results observed in studies in which one single dose was given.

The only difference between the results observed in the studies of Figure 1 and the studies of Figure 2 as to correlation between quinidine plasma levels and intensity of the cardiac effect of the drug* is that only one definite discrepancy between plasma level and intensity of cardiac effect was observed: In the eighth study, the cardiac effect four and seven hours after the last dose of quinidine was the same in intensity whereas the corresponding plasma levels were, respectively, 2.7 mg. and 2.1 mg. per liter. The difference between the results obtained in the two sets of studies may be more apparent than real. Indeed, had we followed our patients longer in the eighth, ninth and tenth studies, i.e., as long after the last dose as we followed them after one single dose in the first seven studies, it is possible that more marked discrepancies would have been observed.

Although the relationship between plasma and heart muscle concentration of quinidine has not as yet been established, it seems profitable to consider a number of factors that theoretically may be responsible for the discrepancies observed between the quinidine plasma level and the intensity of the effect of the drug on the heart. It may be first postulated that when, due to the action of quinidine, the rate of the auricular circus movement has been lowered to a certain level and has remained at the same level a few hours later, the concentration of the drug present in the auricular muscle remains approximately constant. For example, in the second study, the circus rate

* Comparison between the intensity of the cardiac effect of quinidine when it is given in single and in repeated doses without attempting to correlate the cardiac effect to plasma levels is the subject of a previous paper now in press.

was 285 per minute two hours and 292 ten hours after the administration of 0.8 Gm. of quinidine sulfate. Although at these two moments the quinidine plasma level was, respectively, 2.6 mg. and 1.3 mg. per liter, it might be assumed that the concentration of quinidine in the auricles was the same. If so, the reason for the discrepancy between tissue level and plasma level is not clear. *A priori*, it could be due either to a plasma level relatively higher than the tissue level two hours after the administration of the drug or to a plasma level relatively lower than the tissue level ten hours after the administration of the drug. If the plasma level, soon after the administration of the drug, is relatively higher than the tissue level, it is possible that at the plasma level observed the auricular tissue has fixed all the quinidine it can. The nature of this process of fixation and the laws that govern it are clearly beyond the scope of this investigation. It also may be that a time factor is involved and that the period during which the auricular muscle was exposed to the high plasma level of quinidine was too short to allow the establishment of as high a tissue level as could be expected from the plasma level. The two explanations do not exclude one another. In short, if the discrepancy between tissue and plasma quinidine levels is due to too high a plasma level during the first few hours that follow the drug administration as compared to its tissue level, it could be due to the fact that the auricular muscle has fixed all the quinidine it can at the plasma levels observed and with the time during which the auricles were exposed to such plasma levels. Another explanation, not exclusive of the first possible explanation just mentioned, is that the plasma level is too low in relation to the tissue level when the plasma level of the drug decreases. This will occur if the heart retains quinidine longer than the plasma and the fifth, sixth and seventh studies seem to suggest this as a definite possibility if the initial postulate is correct that equal cardiac effects mean equal concentration of quinidine in the heart muscle.

On the other hand, the postulate originally made that equal cardiac effects mean equal cardiac quinidine concentrations may very well not be correct. In the second study for example, although the cardiac effect is of the same intensity two hours and ten hours after the administration of the drug, the cardiac concentration of quinidine two hours after the drug administration may well be different from that ten hours after the administration. If the concentration of quinidine in the auricles two hours after the administration of the drug is higher, it would seem that the cardiac effect is not more marked after two hours because there is a maximal cardiac response to quinidine beyond which a further increase in the cardiac concentration of quinidine produces little or no further effect on the heart. Whether or not the problem is further complicated by the fact that all or part of the effect of quinidine is due to its products of degradation and the intensity of its effect determined therefore by the rate of degradation, it is not possible to state from these experiments. Furthermore, the possibly active degradation products of quinidine may not be fluorescent, which would be another complicating factor, as the method we used to determine the quinidine concentration in plasma and tissues is based on the property of quinidine of being fluorescent.

To summarize, as explanations for the discrepancies observed between the plasma quinidine level and the intensity of the cardiac effect of the drug, there are several possibilities: (1) the plasma level in the first few hours after the oral administration of the drug is too high as compared to its auricular level because the auricles become saturated at relatively low plasma levels; (2) the plasma level in the first few hours is too high as compared to its auricular level because the time during which the auricles are exposed to a high plasma level is too short and therefore the auricles do not fix as much quinidine as might be expected from the height of the plasma level; (3) the plasma level later in the period of action of the drug is too low as compared to its

auricular level because the auricles retain quinidine longer than the plasma and (4) the auricular level early in the period of action of quinidine is commensurate with the plasma level but the cardiac effect is not more marked because the increment of the

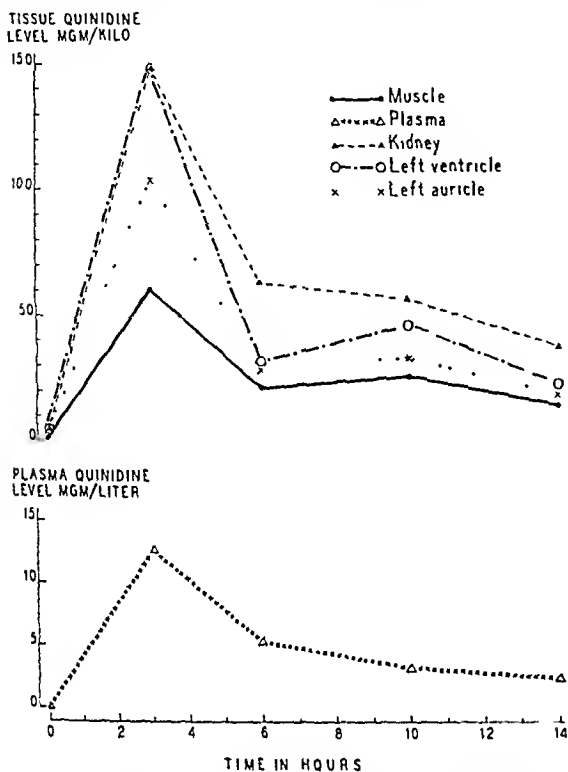


FIG. 4. Arterial plasma quinidine level expressed in mg. of the base per liter, and quinidine levels expressed in mg. of the base per Kg. in striate muscle, left auricle, left ventricle and kidney in five dogs at the time they were sacrificed. One dog was used as a control, received no quinidine and was sacrificed at 9 A.M. The other four received 50 mg. quinidine sulfate per Kg. of body weight at 9 A.M. and were sacrificed respectively three, six, ten and fourteen hours after the administration of quinidine.

cardiac effect decreases and tends toward zero with any further increment of the auricular level.

STUDIES MADE ON DOGS

Method. To determine which of the explanations mentioned is responsible for the discrepancies between the quinidine plasma level and the intensity of the cardiac effect as measured by the effect on the rate of the circus in auricular fibrillation, a series of experiments was performed on dogs in an attempt to establish the relationship between quinidine plasma level and quinidine

tissue level. Plasma and tissue quinidine levels were determined with the method referred to previously.¹ First, a series of five dogs was used. All the dogs fasted for twenty-four hours and were fed ground meat at 9 A.M. One dog, used as a control, received

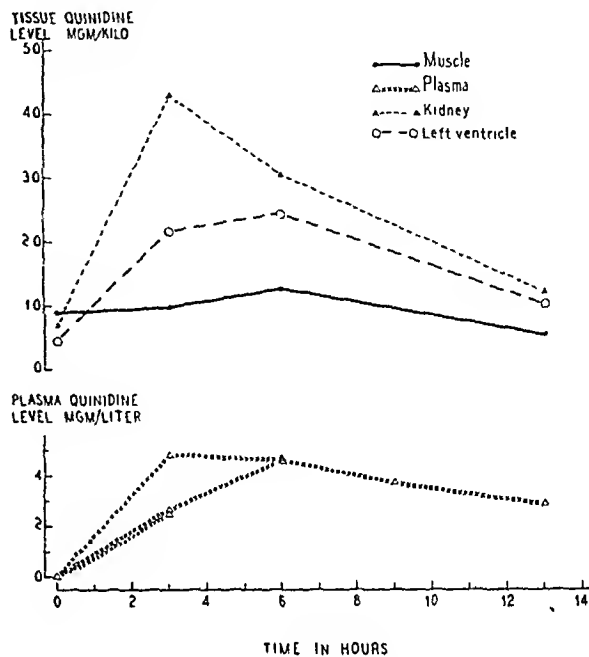


FIG. 5. Venous (four determinations of quinidine plasma levels simultaneously in arterial and venous blood yielded the same results) plasma quinidine level expressed in mg. of the base per liter and quinidine levels expressed in mg. of the base per Kg. in striate muscle, left ventricle and kidney in four dogs at the time they were sacrificed. One dog was used as a control, received no quinidine and was sacrificed at 9 A.M. The other three dogs received 25 mg. quinidine sulfate per Kg. of body weight at 9 A.M. and were sacrificed respectively three, six and thirteen hours after the administration of the drug. In the dog killed six hours after the administration of the drug the plasma quinidine level was also determined three hours after the administration. In the dog sacrificed thirteen hours after the administration of the drug the plasma quinidine level was also determined three, six and nine hours after the administration of the drug.

no quinidine; the other four received in their meat 50 mg. quinidine sulfate per kilo of body weight. The control dog was immediately anesthetized by an intravenous injection of 2 cc/kilo of a 20 per cent solution of sodium barbital. One-half hour after the injection, a sample of arterial blood was drawn from the femoral artery and samples were taken of the striate muscle and kidney. The chest was immediately opened and

samples of left auricle and left ventricle muscle were taken. The time necessary for all samplings ranged from three to seven minutes, generally four or five minutes. The dogs that received their quinidine at

As 50 mg. of quinidine sulfate per kilo of body weight is a definitely higher dose than the doses previously used in the studies on human beings, a similar experiment with smaller doses of quinidine was performed

TABLE II*

Dog No.	Plasma Quinidine (Mg./Liter)	Leg Muscle Quinidine (Mg./Kilo)	Kidney Quinidine (Mg./Kilo)	Left Ventricle Quinidine (Mg./Kilo)	Left Auricle Quinidine (Mg./Kilo)
1. Control	0	1.1	4.4	4.4	4.5
2. Sacrificed 3 hours after drug administration	12.5	60	148.4	148.6	104.1
3. Sacrificed 6 hours after drug administration	5.2	20.7	62.5	31.8	27.2
4. Sacrificed 10 hours after drug administration	3.2	25.3	56.9	45.9	32.9
5. Sacrificed 14 hours after drug administration	2.4	14.8	37.4	23	17.7

* Arterial plasma and tissue quinidine levels (expressed in mg. of the base respectively per liter of plasma and per kilo of tissue) in five dogs. Dog No. 1 was used as a control, received no quinidine and was killed at 9 A.M. Dogs 2, 3, 4 and 5 each received orally 50 mg. quinidine sulfate per kilo of body weight at 9 A.M. and were sacrificed respectively three, six, ten and fourteen hours after the administration of the drug. Blood samples and tissue samples were taken at the time the dogs were sacrificed.

TABLE III*

Dog No.	Plasma Quinidine (Mg./Liter)	Leg Muscle Quinidine (Mg./Kilo)	Kidney Quinidine (Mg./Kilo)	Left Ventricle Quinidine (Mg./Kilo)
1. Control	0	8.9	6.9	4.5
2. Sacrificed 3 hours after drug administration	2.4	9.8	42.8	21.7
3. Sacrificed 6 hours after drug administration	4.8			
3 hours after drug administration	4.6	12.6	30.3	24.6
6 hours after drug administration	2.5			
4. Sacrificed 13 hours after drug administration	4.6			
3 hours after drug administration	3.7			
6 hours after drug administration	2.9	5.6	12.0	10.3
9 hours after drug administration				
13 hours after drug administration				

* Venous plasma and tissue quinidine levels (expressed in mg. of the base, respectively, per liter of plasma and per kilo of tissue) in four dogs. Dog No. 1 was used as a control, received no quinidine and was killed at 9 A.M. Dogs Nos. 2, 3 and 4 each received orally 25 mg. quinidine sulfate per kilo of body weight at 9 A.M. and were killed respectively three, six and thirteen hours after the administration of the drug. Blood samples and tissue samples were taken on all dogs at the time they were sacrificed. Plasma levels were also determined for dog No. 3, three hours after the administration of quinidine and for dog No. 4, three, six and nine hours after the administration of quinidine.

9 A.M. were anesthetized, respectively, at 11:30 A.M., 2:30 P.M., 6:30 P.M. and 10:30 P.M. and were killed at 12 noon, 3 P.M., 7 P.M. and 11 P.M., respectively, i.e., three, six, ten and fourteen hours after the ingestion of quinidine. (Fig. 4 and Table II.)

on a series of five dogs; one dog was again used as a control and received no quinidine whereas the other four received 10 mg. quinidine sulfate per kilo of body weight. The dogs were killed according to the schedule used in the first experiment. The

quinidine plasma levels were all very low, i.e., 0.0 mg./liter in the control dog and 0.1, 2.1, 0.5 and 2.8 mg./liter in the dogs fed quinidine and killed three, six, ten and fourteen hours, respectively, after the ingestion of quinidine. The quinidine tissue levels also were very low, in fact not higher in the dogs fed quinidine than in the dogs used as controls in this series as well as in the first series.*

A third experiment was performed on a series of four dogs. One served as a control; the other three were fed 25 mg. quinidine sulfate per kilo and were killed, under anesthesia, three, six and thirteen hours after the administration of the drug. Plasma and tissue quinidine levels (striate muscle, kidney, left ventricle) were determined on samples taken when the dogs were sacrificed. In addition, plasma levels were also determined for the dog killed six hours after the ingestion of quinidine, three hours after the administration of the drug and for the dog killed thirteen hours after the administration of quinidine, three, six and nine hours after the administration of the drug. (Fig. 5 and Table III.)

Results and Discussion. When dogs received 50 mg. quinidine sulfate per kilo, maximal plasma and tissue quinidine concentrations were reached within three hours after the ingestion of the drug. Six hours after the ingestion, there was a sharp decline both in the tissue levels and the plasma level. Ten and fourteen hours after the ingestion, there was a tendency toward a slow decrease in tissue and plasma levels. From the frequency of the determinations we cannot say exactly when the maximal tissue and plasma concentrations occurred or how long they remained maximal but it is obvious that the plasma level was high enough, long enough, so that a much higher level was obtained in the leg muscle, kidney, left ventricle and auricle. If we compare Figure 5 with any one of the studies depicted in

Figure 1, study 6 W. H. for example (being fully aware that one study is on a human being and the other one an experiment on a dog, and also that at least the plasma level curves in both types of study are comparable in their general outline) we will see that six hours after the ingestion, (1) there has been a definite decrease of the plasma level in both the patient and the dog and (2) the tissue level has fallen markedly but the intensity of the effect on the circus rate has decreased very little. It seems, therefore, that the first two explanations offered to account for the discrepancies between quinidine plasma level and intensity of its effect on the circus rate are untenable. It can be concluded that whereas tissues fix some quinidine at low plasma concentrations, they do not become saturated with relatively low plasma levels and also that the time during which the auricles were exposed to a high plasma level was long enough for them to fix an enormous quantity of quinidine. It seems, therefore, that the reason why the intensity of the cardiac effect is not more marked early in the period of action of quinidine is that, with any increment of the quinidine auricular level, there is a decrease in the increment of the cardiac effect which tends toward zero with any further increment in the quinidine auricular level. Whether later in the period of action of quinidine, the plasma level is comparatively lower than the auricular level, seems to be improbable as there is no obvious difference in the rate of disappearance of quinidine from the plasma and from the tissues.

An analysis of experiments in which dogs received 25 mg. quinidine sulfate per kilo (Figure 5, Table III) yields essentially the same conclusions. No auricular tissue level was determined in this experiment because of the parallelism noted in the first series of dogs between auricular and ventricular levels.

SUMMARY AND CONCLUSIONS

An attempt was made to correlate the concentration of quinidine in the plasma,

* With the method used to determine quinidine tissue levels, the tissues of the control dogs were found to contain slight amounts of some material indistinguishable from quinidine.

the concentration of quinidine in the heart (auricles and ventricles) and the intensity of the effect of quinidine on the heart.

1. The first problem consisted of studying, in human beings, the correlation between the plasma concentration of quinidine and the intensity of the effect of quinidine on the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. Patients with chronic auricular fibrillation were given orally single and/or repeated doses of quinidine sulfate. The concentration of the drug in the plasma and the intensity of its effect on the rate of the circus movement were followed.

In seven studies in which one single dose of from 0.4 to 0.8 Gm. of quinidine sulfate was given, the intensity of the cardiac effect of the drug and its plasma concentration were found to be grossly parallel but not parallel in a strictly quantitative manner. Indeed, discrepancies between intensity of cardiac effect and quinidine plasma concentration were found, the plasma level of the drug decreasing faster than the intensity of its cardiac effect.

In three studies in which repeated doses (0.4 Gm. every two hours for three or four doses) of quinidine sulfate were given, there seemed to be more parallelism between plasma concentration and intensity of the cardiac effect. This may be more apparent than real because the patients were not followed long enough.

The main possibilities among several theoretical explanations that may explain the discrepancies observed between quinidine plasma concentration and intensity of the cardiac effect were discussed.

2. The second problem consisted in an attempt to correlate in dogs the concentration of quinidine in the plasma and in the

heart muscle. Such experiments showed that the concentration of quinidine in the tissues is much higher than the plasma concentration of the drug. The time at which the highest tissue concentration is reached corresponds with the peak of the plasma concentration. Following the rise there is a rather sudden drop in tissue and plasma concentrations, then a more gradual decrease.

3. If the results observed in the experiments on dogs are applicable to human beings, it would appear that the main factor accounting for the discrepancies observed between quinidine plasma concentration and intensity of the effect on the heart is the fact that the cardiac effect is not proportional to either the plasma or myocardial concentration of the drug. Indeed, any further increase in the heart concentration yields a diminished increment of cardiac effect.

We want to express our gratitude to Dr. David P. Earle and his collaborators at the Goldwater Memorial Hospital, Welfare Hospital, New York City, for their help in doing the quinidine determinations.

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Clinical Evaluation of the Treatment of Pneumococcic Type III Pneumonia*

MORRIS F. COLLEN, M.D. and R. LOWRY DOBSON, M.D.

Oakland, California

THE bacteriologic and clinical characteristics which distinguish type III pneumococcus from other pneumococcic types causing pneumonia are well known. From a practical viewpoint the chief problem confronting the internist has been the resistance of this type of pneumonia to treatment. Type III pneumonia warrants special study, not only because it carries the highest case fatality rate for pneumococcic pneumonia, but because it is one of the most frequent forms of pneumonia. (Table I.)

This study presents comparative results in the treatment of pneumococcus type III pneumonia with various combinations of type-specific antiserum, sulfadiazine and penicillin.

During a three-year period (1942 to 1945), 2,176 consecutive patients with pneumococcic pneumonia were treated at the Permanente Foundation Hospital. The diagnosis of pneumonia was substantiated in every patient by indisputable physical findings or a positive roentgenogram. Patients with pneumonia as a secondary diagnosis to another disease were excluded. Sputum examination in every patient showed the predominant organism to be pneumococcus. Specific typing by the Neufeld method was obtainable in 70 per cent of the patients.

As a cause of pneumonia in this series, the type III pneumococcus was found to be the fourth most frequent etiological organism. (Table I.) In a nationwide survey of the

bacterial etiology of pneumonia from 1938 to 1940, Rumreich¹ found type III to be one of the first four most frequent causes of pneumococcic pneumonia in each of the six representative states studied. (Table II.) Of 16,813 patients with pneumonia compiled

TABLE I
LEADING PNEUMOCOCCIC TYPES AS CAUSES OF DEATH FROM PNEUMONIA, 1942-1945

Pneumococcus Type	No. Cases	No. Deaths	Per Cent Mortality
III	103	21	20.4
II	61	9	14.8
VII	241	31	12.8
IV	106	11	10.4
I	152	81	7.2
XII	79	5	6.3
V	91	5	5.5
XXV	124	5	4.0
All others* . . .	2,073	105	5.1
All cases . . .	2,176	126	5.8

* All cases exclusive of Type III.

by Heffron,² 10.8 per cent were due to this organism.

Among the clinical features which contribute to the high mortality rate for pneumococcus type III pneumonia is its greater incidence among older age groups. This is clearly demonstrated in Table III which shows that over half (51.4 per cent) of all patients with type III pneumonia were over the age of fifty, whereas only about one-fourth (26.8 per cent) of all other types of pneumonia occurred in patients of this older age group. Likewise, only 11.6 per

* From the Department of Medicine, Permanente Foundation Hospital, Oakland, Calif. Statistics compiled by Martha Eaton, A.B. and Margaret Chamberlin.

TABLE II

COMPARATIVE INCIDENCE OF TYPE III PNEUMOCOCCIC PNEUMONIA IN SIX REPRESENTATIVE STATES
(1938-1940)*

California		Colorado		Illinois		Louisiana		Missouri		New Jersey	
Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent
III	13.26	I	16.08	I	19.40	I	22.19	I	18.95	I	20.28
I	11.10	II	15.25	III	13.61	VII	10.64	III	13.68	III	13.94
VII	9.84	III	12.45	II	10.15	>XXXIII	7.02	VIII	8.79	VIII	9.12
VIII	7.19	VII	8.08	VII	8.27	III	6.72	VII	6.32	VII	7.50

* From Rumreich.¹

TABLE III

COMPARATIVE INCIDENCE AND MORTALITY BY AGE

Age (Years)	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
10-19	3	2.9	0	0	121	5.8	1	0.8
20-29	9	8.7	1	6.3	400	19.3	7	1.7
30-39	15	14.6	5	22.7	508	24.6	11	2.2
40-49	23	21.4	9	45.0	488	23.5	31	6.3
50-59	27	26.2	5	31.3	336	16.2	34	10.1
Over 60	26	25.2	1	11.1	220	10.6	21	9.6
Total	103	100.0	21	20.4	2,073	100.0	105	5.1

TABLE IV

COMPARATIVE INCIDENCE AND MORTALITY BY AGE GROUPS, EXCLUDING ASSOCIATED DISEASES

Age (Years)	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
10-30	7	9.0	0	0	411	26.1	7	1.7
30-49	27	34.6	13	48.2	790	50.0	28	3.5
50-70	44	56.4	5	11.4	373	27.6	29	7.8
Total	78	100.0	18	23.1	1,574	100.0	64	4.1

cent of patients with pneumococcus type III pneumonia were under the age of thirty, whereas 25.1 per cent of patients with pneumonia due to other pneumococcic types were in the younger age group. Other studies have found the proportion of pa-

suggests an increased virulence of the organism itself since groups of patients of the same age are compared.

Since the increased fatality rate in older patients might be attributed to the greater frequency of serious associated diseases,

TABLE V

COMPARATIVE INCIDENCE AND MORTALITY BY NUMBER OF PNEUMOCOCCI PER OIL FIELD, BLOOD CULTURE, NUMBER OF LOBES INVOLVED AND LEUKOCYTE COUNT

	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
Sputum Pneumo Count *								
Under 10	13	14.3	1	7.7	481	30.8	2	0.4
11-30	33	36.3	1	3.0	514	32.9	9	1.7
31-74	23	25.3	8	34.8	394	25.2	20	5.1
Over 75	22	24.1	9	40.9	176	11.3	27	15.3
Blood Culture								
Positive	8	7.8	4	57.1	204	9.9	36	17.6
Negative	80	77.6	11	13.7	1,597	77.0	38	2.4
Unknown	15	14.6	6	272	13.1	31	
Lobe Involvement								
Single	68	66.0	10	14.7	1,488	71.8	32	2.2
Multiple	35	34.0	11	31.4	585	28.2	73	12.5
Leukocyte Count								
Under 6,000	12	11.7	10	83.3	76	3.7	31	40.8
6,000-10,000	14	13.6	3	21.4	233	11.2	25	10.7
10,000-25,000	57	55.3	5	8.8	1,105	53.3	25	3.2
Over 25,000	19	18.4	2	12.5	646	31.1	10	1.5
Unknown	1	1.0	1	13	4	
All Cases	103	100.0	21	20.4	2,073	100.0	105	5.1

* Data available in only 1,656 cases.

tients with type III pneumonia over the age of forty to be 60 per cent,³ 69 per cent⁴ and 81 per cent,⁵ as compared to 73 per cent in this series. (Table III.) That this is an important factor in producing the higher gross mortality rates for this series of type III pneumonia is obvious, as the average mortality rate for a group of patients over the age of fifty with pneumococcic pneumonia is several times that for a group under the age of thirty. (Table III.) However, it is apparent from Table III that for each decade the average patient fatality rate for type III pneumonia tended to be higher than that for pneumonia due to other types. This

Table IV presents comparative mortality rates for this series of patients, excluding all patients with associated diseases. About 24 per cent of patients with type II pneumonia and 20 per cent of patients with other types of pneumococcic pneumonia had concomitant conditions.

It is apparent from Table IV that adults with simple uncomplicated pneumococcic pneumonia of any type under the age of thirty have a very low mortality rate. Cecil³ emphasized that even before chemotherapy the mortality was low in those patients with type III pneumonia under the age of thirty. However, patients with type III pneumonia

between the ages of thirty and fifty have an unusually high mortality rate even in the absence of associated diseases. In elderly patients (over the age of fifty), it is suggested that any increase in the fatality rate of type III over pneumococcic pneumonia may very

pneumococci count for type III pneumonia has been questioned,⁶ Table v shows a correlation between an increasing pneumococci count and mortality. Whether the sputum showed few or many organisms for each group so classified, patients with type

TABLE VI
COMPARATIVE INCIDENCE AND MORTALITY BY SEX

	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
Male	95	92.2	19	20.0	1,768	85.3	97	5.5
Female	8	7.8	2	25.0	305	14.7	8	2.6
Total	103	100.0	21	20.4	2,073	100.0	105	5.0

TABLE VII
COMPARATIVE INCIDENCE AND MORTALITY BY DAYS ILL BEFORE ADMISSION

No. Days	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
1	31	20.4	1	5.9	547	26.4	16	2.9
2	17	16.5	2	11.8	396	19.1	16	4.0
3-4	29	28.2	7	24.1	513	24.7	25	4.9
Over 4	34	33.0	10	29.4	555	26.8	37	6.7
Unknown	2	1.9	1	62	3.0	11	
Total	103	100.0	21	20.4	2,073	100.0	105	5.1

well be due to associated diseases, since in the absence of concomitant conditions the mortality rates for this age group were not remarkably dissimilar.

To compare further the severity of the illness in patients with type III pneumonia and pneumococcic pneumonia due to other types, Table v presents data concerning certain important factors influencing prognosis and mortality in pneumonia. The number of organisms in the sputum is an important index of the severity of the infection. Although the reliability of the sputum

III pneumonia had higher mortality rates than those with pneumonia due to other pneumococcic types. There was also a greater frequency of patients with large numbers of organisms in their sputum among the type III pneumonias than among other types of pneumonia.

Patients with pneumonia without demonstrable bacteremia had much higher mortality rates for the type III than for other pneumococcic types. (Table v.) Although the incidence of bacteremia was apparently the same in both groups, patients with type

III pneumonia and bacteremia showed over three times the fatality rate for that of other pneumococcic types. The extent of pneumonia is an important factor influencing mortality and Table v shows that multiple lobe involvement was approxi-

TABLE VIII
COMPARATIVE LENGTH OF HOSPITAL STAY (EXCLUSIVE OF DEATHS)

	Type III		All Other Types	
	No. Cases	Per Cent Incidence	No. Cases	Per Cent Incidence
<7 days	43	52.5	1,219	61.8
7-14	23	28.0	565	28.9
15-21	8	9.8	88	4.5
22-28	2	2.4	42	2.1
>28	6	7.3	54	2.7
Total	82	100.0	1,968	100.0

mately as frequent in both groups of patients. For either single or multiple lobe involvement patients with type III pneumonia had a much higher fatality rate than those with pneumonia due to other types. Leukopenia is a grave prognostic sign in pneumococcic pneumonia. Table v shows that severe leukopenia (under 6,000 cells per cu. mm.) was three times more frequent in type III pneumonia and had an associated mortality rate of about twice that for pneumococcic pneumonia due to other types. In general, Table v demonstrates that when classified in groups according to similar severity factors, type III pneumonia consistently shows a higher mortality rate than pneumococcic pneumonia due to other types.

That the incidence of pneumococcic pneumonia is greater among males is well recognized; however, Table vi reveals that this difference was even more marked for type III. For either sex, however, the mortality rate was higher for type III than for pneumonia due to other types. The higher incidence of type III pneumonia in females

as reported by Cecil⁸ was not found in this series.

The interval between the onset of pneumonia and the time of admission to the hospital is an important factor influencing mortality. Table vii shows that this was

TABLE IX
COMPARATIVE INCIDENCE OF CERTAIN COMPLICATING CONDITIONS

	Type III		All Other Types	
	No. Cases	Per Cent Incidence	No. Cases	Per Cent Incidence
Sterile effusions.	6	5.7	94	4.1
Empyema	0	0.0	4	0.2
Lung abscess . .	2	1.9	7	0.3
Endocarditis . .	0	0.0	3	0.1
Meningitis	0	0.0	2	0.1

even more striking for type III pneumonia in which the mortality rate for patients who had been ill for three or more days prior to admission was at least four times that of those admitted in the first or second day of illness. By each day of illness at the time of admission the mortality rate for type III pneumonia was higher than that for pneumonia due to other types.

It is further evident from Table viii that patients with type III pneumonia had a tendency to require a slightly longer period of hospitalization for recovery. However, other than a possibly greater frequency of lung abscesses the incidence of common complicating conditions was similar to that found in pneumococcic pneumonia due to other types. (Table ix.)

EVALUATION OF TREATMENT

During the first half of this study, which was prior to the advent of penicillin, patients with pneumococcic pneumonia were treated with sulfadiazine and adjuvant type-specific antiserum when indicated.

Type III pneumococcic antiserum in large doses was used in thirty-three of forty-eight patients (56 per cent). This group of patients was also treated with two different dosage regimens of sulfadiazine, as reported elsewhere.⁷ One group was treated with usual

and in whom the majority also received large doses of serum, the fatality rate was maintained at the exceedingly high rate of 34 per cent.

With the advent of penicillin a second group of patients with pneumococic pneu-

TABLE X
COMPARATIVE MORTALITY RATES BY METHOD OF TREATMENT

Pneu- mo- coccus Type	Sulfadiazine with Adjuvant Serum Therapy						Sulfadiazine with Adjuvant Penicillin Therapy		
	Usual Dose Sulfadiazine			Double Dose Sulfadiazine					
	No. Patients	No. Deaths	Per Cent Mortality	No. Patients	No. Deaths	Per Cent Mortality	No. Patients	No. Deaths	Per Cent Mortality
III	11	2	18.2	47	16	34.0	46	2	4.3
II	22	6	27.3	10	2	20.0	29	1	3.4
VII	68	20	29.4	92	10	10.9	81	1	1.3
IV	34	5	14.7	31	4	12.9	41	2	4.2
I	29	4	13.8	52	6	11.5	71	1	1.4
XII	14	2	14.3	30	2	6.7	35	1	2.9
V	11	2	18.2	45	2	4.4	35	1	2.9
XXV	26	3	11.5	55	1	1.8	43	1	2.4

doses of sulfadiazine (8 Gm. daily, maintaining average blood levels of 8 to 10 mg. per 100 cu. cm.) and a second group, demonstrated to be of comparable severity, was treated with double these doses (maintaining blood levels of 12 to 20 mg.). It was shown that a general decrease in the mortality rate occurred in all types of pneumococcic pneumonia receiving the double dose, *exclusive* of type III. (Table x.) It was also pointed out that the group of patients with type III pneumonia receiving double doses of sulfadiazine also had received type III antiserum in 14 per cent more instances than those with usual doses. As is indicated in Table x the increased use of serum and /or the increased dosage of sulfadiazine were ineffectual in reducing the mortality of type III pneumococcus pneumonia. In the group of forty-seven patients with type III pneumonia, who received very large doses of sulfadiazine

pneumonia, demonstrated to be of comparable severity, were treated with sulfadiazine and penicillin.⁸ Of forty-six patients with type III pneumonia in this group, twenty-seven (58 per cent) were classified as being seriously ill and were treated with both penicillin and sulfadiazine with a resultant mortality rate of 7.4 per cent. (Patients similarly classified and treated with both specific antiserum and sulfadiazine had a mortality rate of 50.0 per cent). The gross mortality rate for patients with type III pneumonia treated with sulfadiazine and adjuvant penicillin was 4.3 per cent. (Table x.) Penicillin was administered most frequently in doses of 25,000 units intramuscularly every three hours. Severely ill patients received 40,000 units intramuscularly every three hours or 10,000 units per hour by continuous intravenous drip. Penicillin therapy was usually continued until

the patient was afebrile at least forty-eight hours. Other details of treatment of these patients have been outlined elsewhere.⁹

SUMMARY AND CONCLUSIONS

In a series of 2,176 consecutive patients with pneumococcic pneumonia, type III was one of the most frequent forms and carried the highest mortality rate. When compared in groups according to similar severity factors, type III pneumonia constantly showed a higher subject fatality rate than that for pneumococcic pneumonia due to other types. Penicillin was the most effective agent in the treatment of pneumococcic type III pneumonia. Sulfadiazine and type III antiserum were relatively ineffectual in any dosage against this type of pneumonia.

Patients with pneumococcic type III pneumonia classified as severely ill who were treated with large doses of both specific antiserum and sulfadiazine had a gross fatality rate of 50 per cent. Patients similarly classified and treated with penicillin and sulfadiazine had a mortality rate of only

7.4 per cent. In this series the gross mortality rate for type III pneumococcic pneumonia prior to the advent of penicillin was 29.3 per cent; with penicillin therapy the mortality rate was 4.3 per cent.

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Mechanisms of Action of Serum Albumin Therapy in Internal Medicine*

S. HOWARD ARMSTRONG, JR., M.D.†

Boston, Massachusetts

IN the last two decades accumulating evidence has cast doubt on the concept (familiar as Starling's hypothesis) that the volume of extracellular extravascular fluid is determined by the balance of capillary hydrostatic filtration pressure against osmotic pressure of plasma proteins and tissue pressure.

The nephrotic syndrome provided an early source of this doubt in the finding that spontaneous diuresis is initiated and edema begins to disappear with no change in the level of plasma proteins.^{1,2} More recently, in cirrhotic patients, identical total protein and albumin levels in the presence and following disappearance of ascites have been reported.^{3,4} Again, normal protein levels noted by groups studying nutritional edema due to war starvation have been supplemented by findings by Ancel Keys and co-workers in nutritional edema experimentally produced.⁵ Unaware of Govarcts' extensive direct measurements of osmotic pressures in famine edema far lower than expected from Howe serum albumin determinations,^{6,7} Keys has interpreted the apparent lack of balance of calculated osmotic and filtration pressure to suggest that an occasionally disturbed equilibrium is not a suitable concept for the relation of intravascular to extravascular water.

The techniques underlying most of the older experimental evidence relating plasma proteins to water balance have had the

common aim of lowering osmotic pressure. Human albumin in large quantities has recently, and for the first time,⁸ permitted the controlled upward variation within wide limits of the osmotic properties of plasma by the substance chiefly responsible for it in the normal state.⁹ This albumin, together with other fractions of plasma of different chemical and biologic properties, is now becoming available to investigators through a national blood collection and fractionation program under the American Red Cross. This presentation undertakes to review the evidence that has emerged in this clinic on the subject of mechanisms and clinical indications in civilian practice in the light of findings in other clinics and to suggest avenues for further investigation.

CIRRHOSIS OF THE LIVER

Spontaneous variability of water balance in the chronic diseases of the kidney and liver necessitates extremely careful selection and prolonged observation of patients before and after therapy to insure validity of correlations between therapy and measurable changes and to prevent waste of valuable material in uninterpretable clinical situations.

The arrest of cirrhotic ascites, first recorded in the early studies of Jancway and co-workers,¹⁰ was interpreted correctly with great caution. Subsequently, Gibson, in the course of testing large quantities of albumin

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School. About one-half of the albumin in the studies herein reported was given in the course of testing the first products of the Massachusetts Biological Laboratory. The remainder was derived from the pyrogen testing of lots made available by the Red Cross for clinical investigation or by direct assignment of such material.

† Welch Fellow in Internal Medicine of the National Research Council.

for the Navy, encountered further instances of ascitic arrest.¹¹

In the past year Dr. Kendall Emerson and the author have subjected this phenomenon to detailed analysis in two patients suffering from severe stabilized hepatic cirrhosis who, over protracted periods of observation, failed to show serum albumin increases on nutritional therapy. This type of patient was chosen because Patek and Post¹² have shown that such a failure of albumin response indicates hepatic damage of gravest prognosis.

Using an initial total dose usually over 700 Gm. of albumin at a rate over 50 Gm. per day, the time required to stop ascites formation (approximately two weeks) is far lower than has been observed with other therapies. (For the most recent of these, "Rockefeller liver," Hoagland⁴ and his colleagues have reported times varying between six months and a year.)

Measurements of the effective serum osmotic pressure* (i.e., the pressure developed by serum against the protein-containing ascitic fluid simultaneously obtained) have indicated that when this variable is above a critical level (differing in various patients) ascitic formation ceases; when below this critical level, ascitic formation resumes.

Rates of ascitic formation have been determined by repeated taps carried out on a full but not distended abdomen. Distention, by influencing hydrostatic pressure in the peritoneal cavity can, in turn, influence formation rates. Thus, our findings in cirrhosis do not pertain to any diuretic effect of intravenous albumin but rather to its effect in prevention of ascites. Such ascitic fluid as formed before or during therapy has always been removed by a needle, not through renal water excretion.

In Gibson's studies¹¹ the water was not emptied by paracentesis before therapy. In his successful cases the water removed from the abdominal cavity was presumably ex-

*We are indebted to Professor George Scatchard, Research Laboratory of Physical Chemistry, Massachusetts Institute of Technology, for making available the facilities with which we have carried out these measurements.

creted by the kidneys. The periods required for ascitic arrest were somewhat longer than in our series of patients.

The evidence thus far accumulated does not mean that albumin will be effective in every cirrhotic patient. It is quite conceivable that in an occasional patient with severe mechanical obstruction to portal flow (increased portal capillary permeability), an induced rise in serum albumin will be exactly balanced by a rise in ascitic fluid albumin, the effective osmotic pressure will not change and the ascites will remain. Janeway¹³ observed a patient with childhood cirrhosis in whom, on albumin therapy in the absence of taps, ascitic fluid protein rose as high as 6 Gm. per cent. Patek¹⁴ likewise observed exactly parallel rises in serum and ascitic fluid osmotic pressures following albumin dosage somewhat less in amount than was employed in our own studies.

However, before a patient is deemed unamenable to albumin, therapy should be carried out with the patient tapped dry for the following reason: Water removal without simultaneous protein removal from the peritoneal cavity yields a concentration of ascitic protein and thus, for given plasma osmotic pressure, a decreased effective pressure. When both ascitic water and ascitic protein are removed together through a trochar, this cannot occur. We have recently observed extremely slow disappearance of ascites on albumin therapy from an ascites-loaded patient in whom, without immediate change in serum osmotic pressure, no fluid reformed after tapping was performed.

Maintenance dose, estimated from rates of decline of serum osmotic pressure, will vary according to the severity of the disease between 20 Gm. a week for a patient with severe cirrhosis to 100 Gm. a week for a patient with terminal cirrhosis. Administration can be carried out easily at weekly or greater intervals in the office or clinic.

There is as yet no reliable evidence that albumin influences any manifestations of cirrhosis other than water balance. Control of ascites has been achieved in hepatic

coma without the slightest apparent effect on the coma. Furthermore, albumin is no substitute for nutritional therapy which in past years has given the first advance in prognosis of some patients with cirrhosis. Indeed, it is to be hoped, from Hoagland's⁴ recent studies, that in many cases intensive nutritional therapy may permit resumption of spontaneous albumin formation by the patient and thus discontinuance of parenteral albumin within a year or so after initial decompensation. The chief value of albumin in cirrhosis will probably lie in its capacity to rid promptly the patient with early decompensated cirrhosis of the heavy disabilities of being water-logged.

IDIOPATHIC HYPOPROTEINEMIA

There is a small, ill defined group of patients who, despite lack of evidence of renal or hepatic disease, present edema and low plasma protein levels quite intractable to administration of high protein diets. The mechanism of this disorder, not as yet elucidated experimentally, has been ascribed to defects in protein absorption or synthesis.¹⁵⁻²⁰

Patients of this type, whom we have studied at the Peter Bent Brigham Hospital in the last five years,²¹ have had in common plasma protein electrophoretic schlieren diagrams reminiscent, in low albumin and gamma globulin components,* of the diagrams characteristic of the nephrotic syndrome; resemblance to nephrosis extends to low urine sodium outputs,† edema fluid proteins below 0.25 per cent (chiefly albumin on electrophoresis) and normal liver function tests; there has however been no significant albuminuria.

The response of two of these patients to intravenous salt-poor albumin has been strikingly different. In one whose moderate edema was of three years' standing, 250 Gm.

over five days yielded a sustained rise of serum osmotic pressure from an initial 125 mm. H₂O to 415 mm. H₂O (normal 375 mm. H₂O) and diuresis of sodium and water with complete loss of edema. The protein level of the last visible edema fluid was below 1 Gm. per cent. Therapy in this amount served to maintain the patient edema-free for over two months. A comparable quantity of albumin immediately removed the first traces of reaccumulating edema at the end of this time.

Another patient, incapacitated by enormous anasarca which for two years had failed to respond to nearly all known diuretic regimens, experienced her first diuresis (15 Kg. weight loss) in a thirty-day period during which 750 Gm. of salt-poor albumin were administered.

At the end of this period, despite continued albumin, her weight curve flattened, her sodium output (which had risen from a base line of under 1 mEq. to over 150 mEq. a day in the first week of therapy) declined. It was apparent that the albumin had lost its initial diuretic effect. At this time it was found that the protein content of the edema fluid had increased tenfold to 3 Gm. per cent (almost pure albumin by electrophoresis). Nearly all the administered albumin could thus be accounted for.

By consequence, although the absolute serum osmotic pressure (measured against saline) had greatly increased during therapy, the effective serum osmotic pressure (measured against edema fluid) actually decreased which was a direction of change exactly opposite to that encountered in treating cirrhosis. Moreover, at the beginning of the therapy period, sudden introduction of 50 Gm. albumin into the circulation yielded an increase in plasma volume sufficient to maintain an almost unchanged osmotic pressure; at the end of the therapy period the same dose resulted in a rise of osmotic pressure without significant increase in plasma volume.* That the first type of re-

* In cirrhosis of the liver the gamma globulin component is usually elevated.

† We are indebted to Dr. William Wallace of the Children's Hospital for his generous collaboration in the many sodium analyses made in this study which have been possible through the flame photometer of his construction.

* The following hypothesis is suggested for the mechanism of these two types of response: Iso-osmotic addition of albumin occurs when the plasma osmotic and mean filtration pressure are almost balanced, such that a

sponse (iso-osmotic addition of albumin) was almost uniformly followed by diuresis of sodium and water and that the second type (isometric addition of albumin) was almost never followed in a like manner, suggests that the diuretic action of albumin in the hypoproteinemic state is related to sustained plasma volume increase.* Studies made on a patient with constrictive pericarditis, next to be considered, further suggest that such an increase is a necessary but not sufficient condition for diuresis. These suggestions will be carried through our consideration of the mechanism of action in the nephrotic syndrome.

The findings in these two patients indicate that "idiopathic hypoproteinemia" can be subdivided into at least two syndromes, perhaps unrelated. In the first, capillary permeability to albumin is not deranged, effective serum osmotic pressure may be brought to normal and disability consequent to edema entirely obviated by intravenous albumin in reasonable dosage. In the second, the primary effect is an increased permeability of peripheral capillaries to albumin.†

A small further increase in osmotic pressure is enough to shift water immediately out of the interstitial compartment; isometric addition occurs when plasma osmotic pressure is already lower than mean filtration pressure and filtration out of the blood stream is in point of fact taking place (as shown by increasing edema); in this instance a considerable rise in osmotic pressure is required before equilibrium is reached and passed, such that reversal of flow, with consequent increase in plasma volume, can occur.

The chief obstacle in the precise verification of this hypothesis is the difficulty in experimentally determining a significant figure for *mean tissue pressure*. This variable, which assumes great significance in the Warren-Stead hypothesis²² of cardiac decompensation edema, has been perhaps most reliably estimated locally by Landis²³ in acute experiments and by indirect means. The use of Landis' quantitative relationship between acutely produced edema and tissue pressure is almost certainly invalid in treating chronic edema.

A second variable impossible of precise measurement in human disease is rate of lymph flow, the effect of which will be to remove fluid from a region into which filtration is taking place.

* That this diuresis is not related to rate of change of plasma volume has been shown in producing equivalent shifts, both in size and speed but not in duration, by glucose *without* diuresis of salt and water.

† Dr. Irving Simons of New York has extensive unpublished studies on another instance of this phenomenon.²⁴

Short of correction of this defect, effective therapy will probably require a range of molecular weights far greater than albumin (69,000) to avoid protein loss into interstitial fluid and to raise effective plasma osmotic pressure.

CONSTRICTIVE PERICARDITIS

An almost constant feature of the syndrome of constrictive pericarditis is hypoalbuminemia. This is generally believed to augment the effect of high venous pressure in producing chronic edema. In general, a high protein diet in the preoperative state has had very little effect on protein level; in the postoperative state (if the operation has been successful) response to diet is usually very slow.

Intravenous administration of large quantities of albumin in one patient has permitted analysis of the interaction of plasma osmotic pressure and plasma volume and venous pressure in the pathogenesis of edema in various stages of this syndrome.*

Preoperatively, the patient's plasma osmotic pressure was about one-half and the venous pressure somewhat over twice the respective normal values for these variables. The restoration of osmotic pressure to normal by some 600 Gm. albumin in three weeks was paralleled by a striking rise in venous pressure and blood volume. There was, however, no weight loss; no urinary diuresis of sodium or water. There was no leakage of albumin into the edema fluid, in contrast to the situation in one type of idiopathic hypoproteinemia. At the end of the preoperative period of albumin therapy response to sudden addition of 50 Gm. of albumin was essentially isometric; the consequent rise in osmotic pressure of the serum was almost precisely balanced by a rise in venous pressure; there was little further increase in plasma volume and analysis of multiple, four-hourly urine specimens showed no transient increase in sodium output.

* We are indebted to Dr. Eugene Eppinger and Dr. Robert Gross for their advice and collaboration in the study of this patient.

In the first three postoperative weeks plasma osmotic pressure fell to less than two-thirds of normal. Response to a sudden injection of 50 Gm. albumin differed from the preoperative response chiefly in venous pressures under 125 mm. saline; although plasma volume increased somewhat with the induced, rapid rise of osmotic pressure to five-fourths normal, no transient diuresis of salt or water was observed. However, after administration of some 300 additional Gm. of albumin in six days, for the first time in the patient's course urinary sodium output rose above the previous extraordinarily low maximum of 3 mEq. a day. After 300 more Gm. a daily output of over 50 mEq. was attained. The sodium output continued to approach the normal for the patient's intake after normal osmotic pressure was reached and albumin stopped.

Eppinger and Burwell²⁵ have recently shown a considerable lag between successful pericardectomy and recovery of ability to increase cardiac output in response to stress which constitutes the fundamental physiologic abnormality of the syndrome.²⁶ The findings in the patient herein studied provide strong clinical suggestion that an increase in blood volume induced by albumin cannot set off renal diuresis of salt and water without an increase in cardiac output which may in turn lead to an increased renal blood flow. Whereas our group has not been set up to carry out direct simultaneous measurements of these variables by the cardiac catheter and modern renal clearance methods, such measurements are now clearly indicated to define the relation of these variables and others perhaps now unknown in the diuresis following albumin.

From the standpoint of therapy this patient's case corroborates a similar experience of Janeway and his colleagues in the suggestion that albumin (however conducive to wound healing) will not remove edema preoperatively. Once the fundamental circulatory defect has been obviated by operation, albumin becomes a valuable therapeutic adjunct in permitting restoration of plasma osmotic pressure to normal far more rapidly

than is possible by diet alone and will thus give the patient the fastest edema removal consistent with his circulatory status.

EDEMA OF CARDIAC DECOMPENSATION

Albumin therapy in cardiac decompensation of other than mechanical origin is complicated by the risk of pulmonary edema attending further increase of the already abnormally large blood volume. Moreover, the inability of the kidney in ordinary decompensation to excrete sodium is strongly reminiscent of the behavior of the structurally undiseased kidney in constrictive pericarditis; Warren-Stead hypothesis²² puts these functional abnormalities on the common basis of fixed, low cardiac output. It is thus possible that an increase in plasma volume as a result of albumin may, in the presence of a failing myocardium, simply result in a concomitant rise in venous pressure without diuresis of salt and water. While cautious exploration is in progress with phlebotomy sets in readiness for pulmonary edema, I think that none of our group is as yet ready to specify indications for salt-poor albumin in edema of ordinary cardiac decompensation.

EDEMA OF MALNUTRITION

Whereas we have not had opportunity to study edema of the famine type, we have been able, with a total dosage somewhat less than required in cirrhosis (about 500 Gm.), to remove edema completely from two patients with profound hypoproteinemia due to malignancy. The benefit, although purely symptomatic, has been striking, notably in the presence of cerebral metastasis.

The rapid restoration of plasma osmotic pressure possible by concentrated albumin in such dosage has greatest therapeutic implications in the preparation of nutritionally hypoproteinemic patients for surgery.

NEPHROTIC SYNDROME

The effectiveness of albumin in cirrhosis, as contrasted with the permeable type of hypoproteinemia, is based on the fact that at

least one-sixth of the material administered remains in the circulation to perform osmotic work. Recent studies by Dr. Emerson and myself have served to confirm the earlier experience of this clinic on albumin in the adult (glomerulonephritic) nephrotic state,²⁷ namely, that administration of 25 to 50 Gm. a day usually yields a daily loss between .25 and .50 Kg. of edema with a corresponding increase in the sodium output of the urine. In contrast to cirrhosis, when salt restriction is not necessary, effectiveness in the nephrotic state usually requires rigid restriction of dietary sodium and the use of salt-poor albumin. After the first two or three days of therapy, however, excessive albuminuria balances almost all the albumin administered. After as much as thirty days of therapy, although the plasma albumin may be slightly increased, the serum osmotic pressure remains under one-half the normal value. Dr. Emerson and I have recently encountered instances when urinary excretion of parenteral albumin is quantitative from the very beginning; in such instances, no diuresis whatever accompanied therapy.

We have seen no evidence of shift in the underlying status of the disease. Following therapy, the plasma albumin level has usually dropped and edema, sooner or later, has re-accumulated. (This experience is in accord with the recent studies of Hutchins, Janeway and their colleagues at The Children's Hospital.) Moreover, in two adults whose glomerulonephritis, although still characterized by nephrotic edema, had progressed to considerable impairment of renal function, intractable uremia followed within a month of albumin therapy. Further experience will be required to determine whether this eventuality is outside the expected incidence in the natural history of the disease. The effect of albumin on renal function is now under examination here and at other clinics.

From the standpoint of mechanism, comparison of the dynamics of spontaneous nephrotic diuresis with the dynamics of diuresis following albumin administration gives best plausibility to the following modified

version of the old view, that the forces governing the accumulation of nephrotic edema relate chiefly to the lowered colloid osmotic pressure of the serum which in turn is due chiefly to renal loss of albumin.

Just as in the initiation of spontaneous diuresis, the diuresis following an initial injection of salt-poor albumin in the nephrotic state (except for a very slight initial rise) proceeds without much change in osmotic pressure.^{28,29} On daily repeated injections a rise in average plasma volume occurs of a magnitude quite comparable to that observed by MacArthur³⁰ in nephrosis during prolonged spontaneous diuresis.

This suggests the following mechanism of spontaneous diuresis: The initiating factor is a decrease of renal permeability to albumin which, in the presence of a constant production rate, leads to an essentially iso-osmotic addition of albumin to the circulation, comparable to that encountered in an albumin injection by vein. That minimal changes in osmotic pressure can effect large transports of water is not surprising from the point of view of equilibrium relations. An analogy replacing chemical potential by gravitational potential is as follows: although water will only run downhill, it takes a very little hill to effect the transport of a large amount of water, presuming the reservoirs on each side and the pathway of the hill are sufficiently big. Govaerts⁷ has independently arrived at a similar mechanism in his analysis of the iso-osmotic diuresis of famine edema.

The exact timing made possible by precipitation of nephrotic diuresis by induced measles³¹ has permitted Drs. Janeway, Hutchins, Wallace and myself to carry out detailed analyses of the dynamics at onset. Our findings corroborate older observations that a rise in plasma osmotic pressure occurs simultaneously with, but does not precede, diuresis of salt and water. The difficulty in obtaining complete urine collections from sick children has thus far blocked attempts to demonstrate large simultaneous decreases in albuminuria in all but one patient. In this patient, albumin

output decreased by a factor of 50 per cent two days before diuresis started. With better collection methods, we are now attempting repeated observations of this type which will be necessary in order to give any validity to a primary rôle for renal albumin permeability.

It is worth pointing out that the tendency of the nephrotic kidney to retain sodium (an old observation, recently re-emphasized by Luetscher³² and sometimes considered a primary tubular defect in nephrosis) may also be a non-specific reaction of functionally normal tubules to profoundly low effective colloid osmotic pressure. Such sodium retention has been produced experimentally in dogs by plasmapheresis;³³ clinically, it is reversible both in profound nutritional edema and in idiopathic hypoproteincemia with normal capillary permeability by albumin therapy. The only edema which requires continuous salt restriction during albumin therapy is in a disease in which such therapy does *not* produce a sustained rise in effective osmotic pressure.

From the standpoint of therapy 1,500 Gm. (representing some 200 plasma donations) is highly uneconomical in order to obtain temporarily 15 to 30 Kg. of water from a patient, even if a process of recovery of albumin from the urine were worked out. The problem of intravenous protein therapy thus turns into a search for means to decrease urinary losses, either by changing renal permeability or by giving (or stimulating the body to produce) a protein of molecular size greater than albumin. Toward the first objective Dr. Emerson and I have administered large quantities of rutin to adults in various stages of nephrosis. A longer series will be required to evaluate this procedure. Toward the second goal massive administration of bigger plasma proteins has not yet been tried.

Rates of loss in the urine of various electrophoretic components, observed both by Luetscher²⁸ and in my own studies,²⁷ suggest that a molecular weight of 100,000 may be too small to be kept in the circulation. Indeed, the predominance of lipid-rich alpha

and beta globulins in the sera of patients with nephrosis may well be due to the fact that gamma and other globulins of like weights (about 160,000) pass into the urine almost as easily as albumin. This is further emphasized by the fact that during spontaneous diuresis induced by measles in the nephrotic syndrome of children, serum albumin and gamma globulin levels all rise simultaneously and at rates roughly proportional to their normal concentrations. It is, of course, possible that there are simultaneous operating defects in synthesis of these components. This can best be determined after experimental settlement of the question of renal permeability shifts.

Clinical similarities between the nephrotic syndrome and the type of idiopathic hypoproteinemia based on increased capillary permeability raises the question as to whether or not these two syndromes are at opposite ends of a continuous spectrum. If this were the case, some degree of increased systemic capillary permeability might be expected in the nephrotic syndrome. The low edema fluid protein levels could be accounted by a small concentration gradient for albumin diffusion due to high urinary loss. To test this possibility in one classical severe nephrotic, Dr. Emerson and I, by huge dosages of albumin, have raised the blood level to approximately 3 Gm. per cent for a period of three days. Daily studies of edema fluid showed protein concentrations always below .7 per cent, a figure not at all comparable to the high levels of albumin in the edema of the idiopathic hypoproteinemia.

REACTIONS TO ALBUMIN

As currently processed and released, concentrated human albumin has a record of almost complete freedom from reactions. In my own experience patients who have experienced nausea, headache and malaise during treatment with certain globin and gelatin preparations have been absolutely asymptomatic on albumin. Occasionally, with doses over 50 Gm. a day mild headache is encountered. Administration in

quantity is obviously contraindicated in patients unable to tolerate consequent blood increases, notably in severe hypertension.

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Seminars on Hypertension

Physiology of Essential Hypertension*

STANLEY E. BRADLEY, M.D.

New York, New York

ELEVATION of the arterial blood pressure has been recognized in man for some fifty years as evidence of an abnormal state that may terminate fatally in congestive heart failure, apoplexy or renal insufficiency. In certain instances hypertension is caused by specific disorders of the kidney, the endocrine system or the brain, but in the majority of cases primary extravascular disease is not demonstrable.

For various reasons different terms have been applied to the latter group from time to time; these include hyperpiesia and essential hypertension, to indicate the importance of the higher intra-arterial pressure, and hypertensive vascular disease to avoid the implication that hypertension is more than one manifestation of an underlying disorder of the vascular system. Although each term is the result of a change in viewpoint, each bears in common the connotation that a single underlying disease entity is at fault. This concept finds support in a fairly uniform natural history and in distinctive anatomic changes. Moreover, a more or less consistent pattern of physiologic change has been identified with essential hypertension, setting it apart from other disorders associated with increased blood pressure. The following discussion is chiefly concerned with the physiology of the disease in man.

SYSTEMIC HEMODYNAMICS IN ESSENTIAL HYPERTENSION

The sphygmomanometer has played an extremely important rôle in making the diagnosis of hypertension a commonplace

in medical practice. The information it yields is incomplete and often inaccurate since only systolic and diastolic pressures can be determined. Continuous accurate recording of intra-arterial pressure may be made by various instruments, such as the Hamilton manometer, the strain-gauge, the Lilly capacitance manometer and the piezo-electric manometer. The tracings so obtained reveal a fluctuating pressure change, a series of pulses each of which presents certain characteristic repetitive phenomena. The systolic and diastolic pressures are but two points, the highest and the lowest pressures, in this cycle. For clinical purposes systolic pressure is defined as the pressure in the occluding arm cuff at which the Korotkow sounds over the brachial artery first become audible as pressure is released, or at which the pulse reappears in the radial artery. Simultaneous pressure determinations by sphygmomanometer and by an accurate membrane manometer indicate that systolic pressures yielded by the former may be 10 mm. Hg lower than the actual value.¹ This discrepancy may be laid to factors such as the area of compression by the cuff, the amount of tissue other than artery compressed and the physical properties of the vessel wall that influence the production of sounds or pulses. Diastolic pressure, on the other hand, taken as the cuff pressure at which the Korotkow sounds suddenly change in character (becoming muffled), is too high by as much as 20 mm. Hg.¹ Hence a somewhat more accurate figure is obtained at the level at which sounds fade away altogether.

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y.

Both systolic and diastolic pressures are elevated in essential hypertension. Characteristic alterations in the pulse wave contour, which may be discerned indirectly in the pulse pressure, also occur. These changes are based upon dynamic alterations in the peripheral vascular bed and cardiac function.

In general, modern concepts of the hemodynamic factors concerned in the regulation of the arterial pressure agree in being based upon Hales' "air-chamber theory" and Poiseuille's laws of fluid flow in small tubes, in one form or another. According to Hales' hypothesis,² blood flows continuously through the vascular system, under a force derived entirely from the activity of the heart, by virtue of the elastic properties of the central arterial reservoir. This reservoir, probably embracing the entire arterial tree to the level of the arterioles, he likened to the air chamber (or Windkessel) of the old fashioned fire pump, in which air under compression maintained a head of pressure upon the water during the input phase of the pump cycle and forced a steady stream of water through the firehose. In the arteries, energy, stored during systolic distention of the arterial reservoir, is believed to return to the blood during diastole in the form of pressure and kinetic energy of flow as a result of the elastic recoil of the arterial walls. Although Hales' analogy is valid in a general sense, it must be applied with caution in a discussion of the physical characteristics of the central arteries, a complex contrasting sharply with the simplicity of the air chamber. Poiseuille's mathematic statement³ of the relation between dimensions of the conduit, flow, pressure, viscosity and resistance in capillary tubes was based upon a study of the behavior of homogeneous, quasi-ideal fluids flowing through rigid tubes at velocities below the critical rates at which turbulence appears. Unfortunately these conditions do not obtain in the circulatory system and the determination of resistance to flow on the basis of Poiseuille's laws is at best approximate. Vascular resistance is usually ex-

pressed as the ratio between the pressure lost through the length of the system and the rate of blood flow through it. This simplified definition requires constancy of viscosity at all rates of blood flow and is vitiated by turbulent flow. It seems certain that the velocity of blood flow seldom exceeds the critical limit⁴ but it is equally certain that blood viscosity may change markedly with minor changes in velocity.^{5,6} Recent investigations⁷ have shown that a linear relation between blood flow and arterial pressure never obtains even in the absence of humoral and nervous vasomotor activity. It has been found that the viscosity change at low velocities arising from the plastic and heterogeneous character of the blood is complemented at high rates of flow by a reduction in frictional resistance due to passive distention of arterioles and capillaries and to the opening of previously non-functioning collateral channels. The interpretation of peripheral vascular resistance in terms of the vascular cross section is approximately correct only when blood flow is constant. Since it has been observed⁸ that the decrement in blood pressure is greatest in the arterioles, change in resistance calculated on the basis of flow and total pressure fall along the vascular bed may be referred to changes in arteriolar vasomotor activity, provided flow is constant.

In hypertensive disease the elevation in arterial pressure is usually ascribed to widespread arteriolar constriction because the total flow of blood through the body (cardiac output) remains within normal limits⁹ and mean arterial pressure (or the average pressure throughout the cardiac cycle) rises. It is recognized that this inference is at best indirect although the facts upon which it is based are incontestable. Cardiac output may be accurately and directly measured today by the Fick method and there is no doubt of the validity of the observation that it remains at a normal level. The change in blood pressure is unquestioned. Other explanations for the increased pressure have been advanced but have proved unsatisfactory. It has been

suggested that more forcible contraction of the heart may impose a greater energy head upon the blood leaving the left ventricle. However, a more violent systolic contraction would be expected to contribute chiefly to kinetic energy and to do so over a shorter space of time unless there is a change in the volume of blood ejected or in resistance to output. In consequence the systolic phase of the cardiac cycle would be shortened, systolic pressure increased and mean pressure changed little if at all. Slight augmentation of the viscosity has been noted¹⁰ but seems too small to account in any significant degree for the change in peripheral resistance. It is possible that undetected changes related to altered velocity may be important in the smaller vessels. Moreover, attention has recently been drawn to the importance of the character of the distribution of erythrocytes in the blood stream. "Sludging" or intravascular agglutination of red cells may cause marked changes in local capillary and arteriolar perfusion.¹¹ Such conglomeration of red cells has been observed in some patients with so-called "malignant hypertension" but there are no convincing data to suggest that this factor is important in the bulk of the patients with hypertensive disease. Pathologic changes in arterioles are often sparse and scattered. Studies of arterioles from muscle and various organs indicate that hypertensive disease is associated with a somewhat more severe grade of medial hypertrophy with or without collagenous degeneration and intimal hyperplasia than one finds in normal individuals of the same age group.¹²⁻¹⁵ This arteriolar lesion occurs frequently in sites that are rarely affected in the normal, such as the kidneys, liver and gastrointestinal tract but it cannot be shown that these changes *per se* impose increased resistance to blood flow. Indeed in some cases it is possible that the lumina are actually increased in diameter. Hence it is necessary to posit active arteriolar vasomotor activity such as one may occasionally observe directly in retinal vessels.

It is generally agreed that the vascular lesions are a manifestation of aging rather than an effect of increased intravascular tension. The fact that pulmonary arteriosclerosis tends to develop only in the presence of pulmonary hypertension has been cited in support of a direct effect of elevated pressure upon the blood vessels,¹⁶ but pulmonary hypertension is not entirely analogous since it is usually associated with stasis and cardiovascular or pulmonary inflammatory disease. Moreover, lesions of the small arteries and arterioles in the systemic system may occur without hypertension; conversely, hypertension of long duration may be associated with little vascular damage. Hence, the two conditions are probably independent. Since arteriosclerosis is usually more severe among hypertensives, it is believed that hypertension may accelerate aging but the conclusion that senescence may predispose to the development of hypertension seems equally valid. Certainly the incidence of the disease increases with age, affecting approximately 40 per cent of the population over the age of fifty.¹⁷ Arteriosclerosis is also more common in these patients than it is in normotensives of the same age. The central arteries become tortuous, dilated and inelastic. Arteriosclerotic disease of the cerebral and coronary arteries ultimately causes death in a large percentage of patients.

The mean arterial pressure is not affected by the changes in the large arteries^{18,19} chiefly because there is an expansion rather than a contraction in the total arterial cross section. Moreover, the arteries probably impose little resistance normally to the flow of blood from the heart to the arterioles.²⁰ Although changes in arterial elasticity do not alter the mean pressure, they do affect the pulse wave contour. It is obvious from what has been said that increased rigidity with decreased distensibility of the arteries would interfere with energy storage during systole. As a result the systolic pressure would increase, other factors remaining constant and the pressure curve would drop sharply during diastole. In such a

case, as in advanced arteriosclerosis of the aorta, the mean pressure would not rise while the diastolic pressure would remain unchanged or fall slightly. Theoretically there is excellent reason to believe that as long as the stroke volume and pulse rate (or cardiac output) remain constant, an increase in the pulse pressure always denotes an augmentation in the arterial elasticity coefficient. In hypertensive disease the pulse pressure is nearly always greatly increased even in the absence of arteriosclerosis. There is considerable disagreement regarding its significance. Studies of pulse wave velocity in the great vessels, on the basis of the classic mathematic formulations made by Moens and later by Bramwell and Hill, of the relationship between the velocity of the pulse transmission along vessel walls and the elastic properties of the vessels indicate a decreased distensibility of arteries in the presence of hypertension. Wiggers and Wégria²¹ attribute this to an active change, probably as a result of muscular contraction in the vessel walls, since they found that the aortic capacity may decrease in dogs during arterial hypertension. Other workers^{22,23} have shown that increased vascular resistance with an elevation of mean diastolic pressure leads to a continuous distention of the arteries that must *per se* reduce further distensibility, perhaps sufficiently to account for the increased pulse pressure of hypertension. This question remains unsettled, particularly since an accurate method of measuring arterial elasticity is lacking. The measurement of pulse wave velocity is often quite difficult technically. Questionable assumptions regarding the length of the vessels and the timing of impulses are required. The analysis of the pulse wave contour is also fraught with uncertainty since many other factors, such as reflected waves, regurgitant flow and altered systolic ejection velocity, may contribute to the observed changes.

The idea that an active vasomotor element may contribute to the observed decrement in arterial elasticity is in harmony with the view that increased motor activity

throughout the entire vasculature is characteristic of hypertensive disease. Since the systemic circulation time remains normal,²⁴ it is probable that there is a normal blood flow everywhere in the body, despite the marked elevation of perfusing pressure, without hyperemia in any significant portion of the vascular bed. Moreover, the blood flow through every major circuit has been measured in patients with essential hypertension without disclosing evidence of selectivity. Certain experiments²⁵ suggest that the musculature of the veins may also partake in the generalized increase in tonus with resultant disturbance of their function as blood reservoirs.

It is frequently asserted that hypertensives are "hyper-reactors" responding to sundry stimuli by excessive elevations of blood pressure and by disproportionate emotional patterns. Clinical experience supports this claim but it has proved difficult to place the phenomenon upon a quantitative footing. Various tests have been devised to elicit hyper-reaction in a standard manner. The pressor responses to immersion of one hand in ice water (4°C.),²⁶ to excitement,²⁷ to the Flack maneuver (prolonged exhalation against 20 mm. Hg pressure)²⁸ and to physical work²⁹ have been widely studied with divergent and conflicting results.^{9,30} In addition it appears that hypertensives may display more striking reductions in blood pressure than normotensives during the pyrogenic reaction²⁵ or following the administration of depressor drugs such as the nitrites^{31,32} and mecholyl.³³ These excessive pressor and depressor responses are usually discussed in terms of vasomotor activity but insufficient data are at hand to permit an accurate appraisal of the hemodynamic adjustments. Obscure changes in cardiac output and in the relation between output and peripheral resistance may be as important in many instances as the intrinsic changes in vasomotion. The behavior of different parts of the vascular bed during these reactions also needs further study. There is little doubt that widespread vasoconstriction or vasodilation

can occur and that the peripheral resistance is not fixed in essential hypertension.

The hemodynamic factors involved in the production of other varieties of hypertension require investigation. Vasoconstriction is probably an important cause of elevated pressure in hypertensive disease of pregnancy, coarctation of the aorta,³⁴ Cushing's syndrome, glomerulonephritis and other forms of renal disease, but careful quantitative studies are too few to permit accurate appraisal. These conditions are to be differentiated from essential hypertension on the basis of manifestations other than the level of the arterial pressure, the character of the pressure pulse contour or the pattern of vascular reactions to stress. The excess epinephrine production of pheochromocytoma may result in a persistently elevated blood pressure closely resembling essential hypertension. However, here characteristic vascular reactions are demonstrable since histamine may elicit a striking augmentation of arterial pressure³⁵ and benzodioxane may have a depressor action.³⁶

Many important advances in the study of human hypertensive disease during the last twenty years have come from studies of individual organ circuits. These studies are important not only because they provide evidence upon which to base conceptual thinking but also because they shed light upon the manner in which arterial hypertension gives rise to tissue damage that may ultimately prove fatal. From the standpoint of prognosis the most important organs affected are the heart, the brain and the kidneys, in the order named. The splanchnic and muscular vasculatures are also important because they may accommodate so large a proportion of the total blood flow, but pathologic conditions in these areas seldom, if ever, develop as a result of hypertension.

THE HEART IN ESSENTIAL HYPERTENSION

Sooner or later, nearly every hypertensive patient presents evidence of cardiac abnormality. The heart increases in size as a result of dilation and hypertrophy of

the left ventricle although the right ventricle may participate in the process. Congestive heart failure may make its appearance insidiously with slowly developing exertional dyspnea, orthopnea and peripheral edema or abruptly with paroxysmal dyspnea and pulmonary edema. Cardiac hypertrophy and decompensation are usually ascribed to increased work; since the cardiac output remains normal in the presence of the elevated mean arterial pressure, heart work apparently increases in proportion to the change in blood pressure. Moreover, work may be enhanced to some extent by an augmented kinetic energy of systolic outflow as a result of more rapid ejection.³⁷ The kinetic energy factor cannot be estimated quantitatively in man but it appears to be of relatively little importance. Effective heart work cannot be calculated on the basis of the product of mean arterial pressure and cardiac output chiefly because it is impossible to measure the mean pressure in terms of periods longer than a few hours. The heart is continuously exposed to the effect of elevated pressure and heart work must be estimated on the basis of the load imposed over a long time in order to evaluate the part it plays in causing cardiac hypertrophy. Single isolated measurements of the blood pressure are useless for this purpose. There is considerable variation in the pressure level from time to time. Perera³⁸ has found that the blood pressure tends to fall and become stabilized at a lower level some time after repeated measurements are begun by the same person. It immediately departs from this level when a stranger takes the pressure or when minor emotional stimulation occurs. Ayman and Goldshine³⁹ found a similar difference between blood pressures taken at home by the properly instructed patient and those taken in the clinic by a physician. The cardiac output is also very variable and even more difficult to follow over any length of time. Finally, current methods of estimating cardiac work fail to make due allowance for the fact that work is performed only during systolic ejection against the changing

pressure head prevailing at the aortic valve, and it appears that a revision of method will be necessary to obtain more accurate values.⁴⁰ Thus it is obviously impossible at present to determine accurately the load under which the heart labors but, nevertheless, it seems likely that myocardial hypertrophy is best explained on the basis of increased work and energy production. Whether cardiac decompensation is the result of a failure of energy production or of a defect in energy utilization remains a debated and unsettled problem.

Another factor that cannot be neglected in considering the pathogenesis of cardiac hypertrophy and decompensation during essential hypertension is the state of the coronary circulation. Disease of the coronary vasculature alone may be sufficient to cause marked hypertrophy and even congestive heart failure. There is little doubt that coronary insufficiency occurs more frequently among hypertensives than among a non-hypertensive population of the same age group.^{9,13} It is generally conceded that this is a result of the acceleration of the aging process by hypertension rather than a direct effect of elevated arterial pressure. Arteriosclerosis is relatively uncommon¹²⁻¹⁴ but arteriosclerosis occurs frequently and leads to myocardial infarction in about 14 per cent of patients with essential hypertension. It seems not unlikely that the coronary arterioles participate in the generalized vasoconstriction characteristic of the disease, but as yet measurements of the coronary flow in man have not been made and the question remains unanswered. There is some evidence that interference with blood flow may account for certain electrocardiographic abnormalities.

Electrocardiographic changes occur in most patients. The so-called "pattern of left ventricular strain," consisting characteristically of inversion of the T wave in the first and possibly the second limb leads usually associated with S-T segment depression and left axis deviation, has been considered by some as typical of the disease.^{41,42} Recent studies^{43,44} have shown

that these manifestations are not related to the severity, duration or character of the blood pressure, to cardiac hypertrophy or to prognosis when the changes due to myocardial infarction and digitalis are eliminated. Most workers^{41,42} consider the strain pattern a result of the pressure stress upon the heart, a view supported by the dramatic return of the ECG to normal following return of the arterial pressure to normotensive levels after lumbar sympathectomy.⁴⁵ However, Filley⁴⁴ has found a fairly good correlation with the presence of arteriosclerosis of the coronary arteries and he suggests that "the relative sufficiency of these vessels is increased by reducing the work of the heart concomitant with the lowering of arterial pressure." He failed to find any prognostic significance in the strain pattern, however, and the significance of the reversal after sympathectomy is unknown because postoperative follow-up has not yet been sufficiently long in most cases. There is evidence that the vascular disease may persist and progress even after the reduction in blood pressure.⁴⁶

Only the left ventricle appears to be subjected to stress during essential hypertension. On direct measurement⁴⁷ the right ventricular pressure in five hypertensives was found to fall within normal limits, indicating the absence of increased arteriolar resistance in the pulmonary bed. The altered ballistocardiographic complex of hypertensive disease probably results from the exaggerated pressure difference between the two ventricles (one expelling blood into a system in which the pressure is elevated and the other into a normotensive system) that leads to asynchrony of ejection and, in consequence, a splintering of the ejection wave ("early M" shaped type).⁴⁸ The venous pressure is normal throughout the course of the disease unless congestive failure supervenes. Hence it may be posited that right ventricular filling is not disturbed and that venous hemodynamics are unaltered. However, the notable tendency of hypertensives to respond to spinal anesthesia,⁴⁹ the pyrogenic reaction²⁵ and in-

creased intra-abdominal pressure⁵⁰ with striking reductions in blood pressure may be based in part upon a defect in the mechanisms that provide for adequate return of blood to the heart.^{51,52}

NERVOUS SYSTEM IN ESSENTIAL HYPERTENSION

Vascular disorders of the central nervous system occur quite frequently in essential hypertension. The catastrophes of massive hemorrhage or thrombosis account for some 15 per cent of deaths due to the disease.⁹ Other less severe manifestations of cerebrovascular disturbances may totally disable many patients. Transient episodes of sensory and motor disturbances, aphasia or amnesia, are seen especially in the accelerated phase, or malignant nephrosclerosis. Headaches are particularly common and disagreeable. These neurologic derangements are by no means peculiar to essential hypertension for they complicate the course of hypertension due to any cause and occur in the absence of hypertension. Thus the following remarks concerning the pathologic cerebrovascular physiology of essential hypertension are probably applicable to other hypertensive states, but since so little is known regarding systemic hemodynamics in these conditions, it is impossible to do more than indicate here the obvious clinical similarities.

The cerebral vasculature suffers the same changes that occur elsewhere in the vascular system. Arteriosclerosis of the large vessels is common although there is no connection between the severity and duration of the elevated blood pressure and the arterial changes.⁵³ Here in contrast to the heart the disease leaves its mark in the arterioles. Intimal hyperplasia, medial hypertrophy and degeneration and occasionally adventitial proliferation are found in varying degree.^{12,14,15,53,54,55} Evidence of active vasoconstriction, somewhat in excess of that in other parts, has been brought forward by Kety and Schmidt.⁵⁶ Using an ingenious method⁵⁷ based on the cerebral uptake of nitrous oxide from the blood, these workers found that cerebral blood flow and cerebral

oxygen consumption were slightly below average normal in all of a series of five hypertensives (mean arterial pressure 143 mm. Hg). Thus in the face of greatly augmented blood pressure, the cerebrovascular resistance doubled, probably because of vasomotor activity, since it seems unlikely that so large an increment in resistance would develop on the basis of the demonstrable arteriolar disease. However, this point must be investigated and evidence of reversibility sought.

The massive cerebrovascular lesions of hemorrhage and thrombosis chiefly involve the larger arteries. Scheinker⁵⁸ has recently called attention to the possibility that venous disturbances may be important. Focal or diffuse lesions of the brain, resulting either from capillary hemorrhage or arteriolar occlusion, frequently give rise to clinical manifestations. One syndrome, characterized by headaches, dysesthesia, fleeting palsies, personality changes, intellectual impairment and a prolonged progressive course, has been described as "chronic hypertensive encephalopathy" by Davison and Brill.⁵⁹ Marked arteriolar disease, leading to widespread areas of demyelination, focal hemorrhages and moderate gliosis, is always found. A more acutely developing clinical complex, of severe headache, convulsions, coma, transient defects of motor activity and sense perception, and a marked elevation in blood pressure ("hypertensive crisis") has been described by Oppenheimcr and Fishberg⁶⁰ who claim that it may develop in the absence of cerebral lesions and that arteriolar spasm alone may be at fault. The evidence for this hypothesis is indirect and inconclusive. The absence of demonstrable disease is rare indeed⁶¹ but it is possible, of course, that vasospasm may be important even when structural changes have occurred. Cerebral edema may develop rapidly and give rise to headache, convulsions and coma without manifestations of focal involvement at any time as part of the picture of acute or chronic encephalopathy. Opinions are varied and contradictory regarding its place in the

pathogenesis of these syndromes.⁶² Studies of cerebral blood flow during encephalopathic seizures are awaited with great interest.

The typical retinal involvement of hypertensive disease may be considered as one manifestation of these encephalopathies since the eye is closely allied in origin to the brain and its investitures. Arteriolosclerosis, characterized chiefly by intimal proliferation and lipid or hyaline deposits, affect the retinal and choroidal arterioles although in the former intimal proliferation is believed to be uncommon.⁶³ A reduction in the caliber of retinal vessels results not only from these lesions but also from vasoconstriction that may develop in localized areas under direct observation.^{64,65} Sclerosis of the common arteriovenous wall at cross-overs may result in partial or complete venous obstruction.⁶⁶ Hemorrhages and areas of degeneration may appear as a result of the vascular lesions.⁶⁶ Edema of the retina and nerve head may occur in association with elevated spinal fluid pressure, but the local vascular disturbances alone may be sufficient to cause edema.^{53,67,68} Diffuse retinal disturbance, occlusion of retinal arteries or veins, and intracerebral involvement of visual centers and pathways may seriously affect sight.

Headache is a common concomitant of these disorders and is one of the most frequent complaints of hypertensive patients even in the absence of demonstrable cerebrovascular involvement. It is occasionally so severe as to prove completely incapacitating, but in most patients it is relatively mild, responding readily to small doses of the common analgesics. The pain is frequently unilateral and migrainous in character. Indeed, it appears to be etiologically related to migraine insofar as both types seem to be caused by dilation and distention of cerebral arteries, particularly the branches of the external carotid. Wolff⁶⁹ claims that pain of this type results from decreased tone of the arteries that leads to greater stretching of the arterial parietes with resultant activation of pain fibers. Many patients give

a history of headache long antedating the appearance of hypertension. It is to be expected that the higher intra-arterial pressure level would result in augmented stretching of the vessels and intensified headache in such persons, whereas in others diminution of tone compatible with comfort at a normal pressure level might prove a cause for pain at a higher intra-arterial pressure. Ligation of branches of the external carotid has been shown to alleviate hypertensive headaches in certain cases.

Personality disorders are commonly associated with encephalopathies but certain changes may occur independently of cerebral disorders. Intensive investigation of the personality pattern in a few individuals suggests that hypertensives tend to display "exaggerated dependent strivings, submissiveness coupled with stubbornness, feelings of weakness and defenselessness, suppression of hostility, fear of injury, and emotional detachment" that may lead to "acute emotional disorders . . . resulting from the inefficiency of the patterns of defense against anxiety and the weakness of repressive mechanisms."⁷⁰ It has been claimed that essential hypertension may be a somatic "manifestation of a psychoneurotic condition based on excessive and inhibited hostile impulses."⁷¹ Unfortunately, studies of large numbers of "normal" persons for purposes of control and of the same individual before and after the onset of hypertension have not been made and do not at present appear practicable. Patients frequently assert that they are more "nervous" and tense following the appearance of hypertension, even when they have not been informed of the presence of the elevated blood pressure. Rest, relaxation and freedom from care have long been known to have a beneficial effect in lowering the arterial pressure. Moreover, elimination of supratentorial activity by general anesthesia or deep narcosis frequently has a striking depressor effect.⁷² The emotional component is so variable from person to person and from time to time that it can scarcely be accorded more than an incidental rôle in the patho-

genesis of essential hypertension. On the other hand, abnormal subcortical activity involving the medullary vasomotor centers or the autonomic nervous system may be very important and may be subject in a measure to influence by higher centers.

Cerebral anemia, increased intracranial pressure and experimental denervation of the carotid sinus will give rise to a sustained arterial hypertension that is apparently mediated through the autonomic nervous system. But there is no evidence that the first two figure prominently in essential hypertension. The physiologic pattern of the last has no proved counterpart in man. Neurogenic hypertension in animals is characterized by a marked increase in cardiac output, tachycardia, augmented blood flow in the extremities and marked lability of blood pressure resulting from fluctuations in cardiac output.^{73,74} Nonetheless, the development of excessive sweating, flushing and whealing, and vasomotor instability in some patients, indicates that autonomic activity may be increased. Dock, Shidler and Moy⁷⁵ have found that decerebration of hypertensive animals results in a return of pressure to normal, despite continued reactivity of the vessels to pressor drugs. They suggest that the medullary vasomotor centers essential in the regulation of arterial pressure may be "set" at higher levels, perhaps initially by the action of some humoral agent. A somewhat similar notion has been put forward by Ogden and his co-workers⁷⁶ who believe that the arterial pressure once elevated is sustained by the action of the sympathetic nervous system. Thus, reduction in blood pressure following high spinal anesthesia,⁷⁶ autonomic blockade⁷⁷ and lumbodorsal sympathectomy⁷⁸ has been considered by some to reflect a specific correction of the hypertensive state through removal of excessive neurogenic vascular stimulation. This conclusion is disputed because the blood pressure is unaffected in a significant proportion of patients, the depressor effect may be transient and vasomotor tone is not specifically reduced in the vasculature of the

extremities and kidneys. But that there is a reduction of total peripheral vasoconstriction and a fall of blood pressure to normal in most patients is undeniable. Hence, it appears that if not granted a primary rôle in the pathogenesis of hypertension, the autonomic nervous system must at least be accounted a major factor in dictating the pressure level.

THE KIDNEY IN ESSENTIAL HYPERTENSION

For many years the kidney has occupied a central position in any discussion of essential hypertension, both because renal disease is so often associated with an elevated blood pressure and because hypertensive disease may terminate in marked renal damage. Moreover, the renal circulation is an extremely important component of the systemic vascular bed. Some 1,200 cc. of blood, or approximately one-quarter of the cardiac output, flow through it each minute.⁷⁹ Because of this large circulation the kidney plays a major rôle as a circulatory buffer. Its vasculature is highly reactive, responding to emotion,⁷⁹ pain,⁸⁰ exercise,⁸¹ blood loss⁸² and the upright position⁷⁹ by vasoconstriction that operates to support the arterial pressure and to provide blood for the perfusion of more needy circuits. Whether defective activity of this kind is concerned in the pathogenesis of essential hypertension or whether it predisposes the renal vascular bed to damage by hypertension is unknown.

Goldblatt⁸³ has brilliantly demonstrated that constriction of the renal arteries causes arterial hypertension in animals either by the production of renal ischemia or by interference with intrarenal hemodynamic adjustments. It appears that a similar mechanism may be concerned in the pathogenesis of some, but not many, instances of human hypertension.⁸⁴ In the remainder, arteriolar constriction and, ultimately, ischemia of renal tissue are clearly demonstrable, but it is impossible to say whether arterial hypertension precedes or follows the vasomotor change.

The clearance methods devised by Homer Smith and his co-workers⁸⁵ for the safe and atraumatic measurement of renal blood flow in human subjects have provided a wealth of information regarding the behavior of renal circulation in the course of essential hypertension. These procedures are based upon the belief that the renal clearance of diodrast or sodium p-aminohippurate (PAH) is a measure of renal blood flow, and require the assumption that all, or almost all, of the measuring substance is cleared from the blood perfusing the kidney. This assumption has proved valid in most hypertensive patients. Analysis of renal venous blood, obtained by venous catheterization during the determination of PAH clearance, indicates 85.4 to 100 per cent extraction of PAH even when renal damage is relatively severe.⁸⁶ Since PAH and diodrast clearances are identical, diodrast must be extracted to the same extent. Hence, data based on the clearance techniques may be used as a basis for discussion of renal circulation in essential hypertension.

In almost one-half of sixty hypertensives studied by Goldring and his co-workers⁸⁷ the renal blood flow was found within normal limits. Only three of these figures exceeded the normal mean value and it was concluded that the renal blood flow tends to be reduced. Intravenous administration of pyrogenic agents evoked a marked increase in blood flow, equal to that observed in normal persons in eighteen of twenty of their subjects. Consequently, a reversible vasoconstriction rather than a fixed vascular obstruction must be called upon to account for the failure of renal blood flow to increase in proportion to the elevation of the arterial pressure under which the kidneys are perfused. Both kidneys are equally affected of the majority of cases.⁸⁸ Unilateral renal or ureteropelvic disease appears to be an uncommon cause of hypertension and unimportant as an etiologic factor in essential hypertension.⁸⁴

Considering the fact that renal blood flow tends to fall within normal limits, ischemia of renal tissue is probably not marked in

most cases. However, ischemia of a part of the kidney may be masked by hyperemia of the remainder. Blood flow must be examined, therefore, in relation to the mass of kidney tissue it perfuses.

The renal tubular tissue can be estimated quantitatively in terms of its maximal reabsorptive and excretory capacities. Diodrast and PAH are excreted with great efficiency when they are present in low concentrations, but at higher concentrations the excretory rate reaches a maximum which appears to be dependent upon the mass of functioning tubular tissue. The maximal rate of transfer from blood into the tubular urine is referred to as the transfer maximum or T_m of the substance in question. Glucose is reabsorbed by a similarly limited transfer mechanism and may be employed to estimate the quantity of tubular tissue processing glomerular filtrate.⁸⁹ Many substances, e.g., most electrolytes, do not lend themselves to this usage because they are handled by the tubular cells in a different manner and are not removed from blood or filtrate at a constant fixed rate, independently of the blood level, above certain relatively high concentrations.

The relation between diodrast clearance and diodrast T_m (blood flow- T_m ratio) has been used to assess the distribution of blood to the renal parenchyma. In most hypertensives this ratio is somewhat depressed below the normal mean figure, but in general it does not deviate greatly from the normal range.⁸⁷ It may be inferred that there is a tendency for relative ischemia to develop. Since diodrast T_m may be normal in many patients with well established hypertensive disease, the ischemic process appears to involve the kidney as a whole without shunting of blood away from a significant mass of parenchymal tissue through by-passes similar to those observed by Trueta and his co-workers.⁹⁰ Even when extensive damage has occurred and diodrast T_m is greatly reduced, the degree of relative ischemia does not appear to be marked. However, there is a suggestion that ischemia may bring about parenchymal destruction

in the observation that diodrast Tm increased more than 10 per cent in seven of twenty hypertensives during the pyrogenic reaction.⁸⁷ This phenomenon may be attributed to more adequate perfusion, during hyperemia, of tubular tissue formerly receiving little blood. Such regions of focal ischemia are also detectable by other means⁸⁹ and it may be surmised that atrophy of tubules with ultimate replacement by fibrous tissue occurs in these sites. Since the extraction of PAH continues to be normal or nearly so, even when extensive parenchymal destruction has resulted in manifest renal insufficiency, blood apparently perfuses normally extracting tubular tissue almost exclusively. Thus cellular dysfunction probably follows upon the withdrawal of the blood supply as a result of vascular constriction and occlusion. In view of the high PAH extraction true arteriovenous shunting must be excluded as a possible cause of localized ischemia. Rather it appears that focal ischemia, possibly resulting from the development of structural lesions, is engrafted upon a state of diffuse ischemia due to vasoconstriction. Although diffuse and focal ischemia are probably of primary importance in producing renal structural damage, they are not necessarily or consistently present in essential hypertension and appear to be consequences rather than causes of the disorder.

The renal functional alterations of essential hypertension correlate well with the pathologic pattern. In about 85 per cent there is no evidence of parenchymal damage and few or moderate changes in the vasculature.¹⁴ In the remainder there is a varying degree of tubular atrophy, associated with occasional hypertrophy, of the proximal segment and fibrosis, which may be sufficiently extensive in occasional instances to produce contraction of the kidney and fine granularity of its surface. The vascular lesions are frequently striking. The small arteries and arterioles show a degree of arteriosclerosis rarely encountered in the normal although from 3 to

17.5 per cent of various series^{12,14,91} fail to present any vascular lesions whatever. The vascular damage is usually not so diffuse that it can be accounted a significant cause of increased resistance to flow. It is characterized by proliferation of the intima, the appearance of subintimal hyaline and lipoidal deposits and hypertrophy of the media. These changes may produce no narrowing of the lumen and may even be associated with dilatation, especially of the afferent arteriole. Glomerular involvement is not striking and obliteration appears to follow destruction of the tubule. Thus atrophic tubules are frequently attached to glomeruli of normal size.⁹³

Glomerular filtration rate tends to remain within normal limits even when renal blood flow is greatly reduced. In part, this maintenance of filtration may be ascribed to the presence of "impotent" tubules that fail to have any excretory activity and serve merely as conduits through which filtrate passes. Such an interpretation is in harmony with the anatomic changes described above. However, the normality of filtration, when blood flow is reduced by vasoconstriction without parenchymal destruction, must involve a local hemodynamic adjustment which operates to increase the filtration pressure so that a normal volume of filtrate is expressed from the smaller minute-volume of plasma. Since arterial pressure is elevated, it may be assumed that the afferent arterioles do not constrict sufficiently to prevent the transmission of the elevated head of pressure to the glomerulus. Hence, the chief locus of vascular resistance must lie in the post-glomerular vascular bed, probably in the efferent arteriole. Lamport⁹⁴ argues, on the basis of mathematic considerations, that afferent arteriolar vasoconstriction is a more important factor. It is possible that this claim is tenable in certain cases in which normal values for filtration and blood flow have been observed, but in the vast majority of patients with essential hypertension efferent arteriolar vasoconstriction must be assigned a major rôle. It has already been noted that intrarenal vasoconstriction may

be eliminated during the pyrogenic reaction.⁸⁷ However, other means of interfering with vasomotor activity have been less successful.

Interruption of autonomic activity by tetraethylammonium bromide,⁷⁷ high spinal anesthesia⁴⁹ and lumbo-dorsal sympathectomy⁹ does not influence the renal blood flow. The fact that the blood flow remains unchanged even when blood pressure is lowered by these means indicates that vasodilation is induced in proportion to the level of arterial pressure, but this phenomenon may be attributed to local autonomous adjustment of the renal circulation rather than to the elimination of vasoconstrictor impulses. Indeed, if the blood pressure is greatly reduced, the renal blood flow may fall markedly. These facts indicate that the renal vasoconstriction of essential hypertension is mediated through a humoral mechanism or local reflex neuromuscular action rather than through nerve pathways. In this connection it is of interest that various pressor agents, including epinephrine,⁹⁵ ephedrine,⁹⁵ paredrinol,⁹⁵ angiotonin⁹⁶ and S-methylisothiurea⁹⁷ evoke a similar renal hemodynamic adjustment.

Certain discrete activities of the renal tubules seem to be specifically affected. Goldring and his co-workers⁸⁷ noted that maximal diodrast excretion was reduced earlier in the disease than maximal glucose reabsorption and they suggested that the underlying intracellular dysfunction might be concerned in some way with the pathogenesis of hypertension. Sodium and chloride reabsorption are also disturbed. As a group hypertensive individuals withstand acute salt deprivation with aplomb in striking contrast to normal individuals.⁹⁸ Perhaps a more efficient sodium reabsorption mechanism accounts for this difference by preventing salt loss during deprivation. However, Farnsworth⁹⁹ has presented evidence that the hypertensive kidney reabsorbs chloride less efficiently than the normal. The discrepancy may arise as a result of either a dissociation between sodium and chloride reabsorption or more

advanced renal damage in Farnsworth's cases, in most of whom glomerular filtration was significantly reduced. The higher urine flows relative to filtration rate among her patients may have been important also in enhancing chloride clearances. In any case an alteration in tubular disposal of sodium and chloride appears to develop in hypertensive disease. This fact, among others, has directed attention to the adrenal cortex.

It is now well known that the adrenal cortex is intimately concerned with the regulation of tubular reabsorption of sodium and potassium. Adrenal cortical insufficiency leads to excessive salt loss with attendant reduction of plasma volume and ultimately fatal shock. Salt replacement and desoxycorticosterone acetate administration brings this situation under control. But continued treatment over a period of years results in the development of hypertension in a high percentage of cases.¹⁰⁰ It has been shown that desoxycorticosterone acetate is the chief offender since control with salt alone is followed by a return of blood pressure to normal. Hypertensive patients, without adrenal cortical insufficiency, respond to administration of desoxycorticosterone acetate by further elevation of blood pressure.¹⁰¹ This reaction occurs in normal persons but it is delayed and less impressive. An adequate salt intake appears to be necessary, since salt depletion prevents the rise in pressure.⁹⁸ It is noteworthy that rigid restriction of salt intake appears to exert a slight depressor effect in hypertensives.¹⁰² These facts suggest that the adrenal cortex may play a part in the pathogenesis of essential hypertension. A search for adrenal cortical lesions has been made but the results have been conflicting and disappointing.

The various disturbances of renal function described above are not easily detected by the means at the command of the clinician. Proteinuria is rather common and increases in severity as the disease progresses. In a small number of cases renal insufficiency may develop and cause death, but in the majority, renal function, as judged by

urinary concentrating power, phenolsulphonphthalein excretion and urea clearance, is not greatly disturbed through the course of the disease.⁹ In most instances of renal insufficiency and uremia the renal parenchymal damage is a result of the development of malignant nephrosclerosis.

This disorder may suddenly appear in previously healthy individuals or in the course of the usual slowly evolving hypertensive process.¹³ The blood pressure rises to a very high level. Congestive heart failure, uremia or a cerebrovascular accident may cut short the course in a matter of months after onset. Uremia always appears apparently as a result of a diffuse necrotizing arteriolitis that chiefly affects the renal arterioles. Here, too, there appears to be intense and widespread renal vasoconstriction which is evident in the marked reduction in renal blood flow. The extraction of PAH has been depressed in three cases of this type studied in this clinic, possibly indicating the operation of arteriovenous shunts or the presence of severely damaged tubular tissue remaining under perfusion. Whether this fatal disorder is simply an intensification of the vascular disease underlying essential hypertension or whether it is an entirely different process remains disputed. A similar acceleration of the evolution of vascular lesions and of renal damage may appear in the course of hypertension caused by glomerulonephritis¹⁰³ or pyelonephritis.¹⁰⁴

The renal functional derangement of essential hypertension appears to be based chiefly upon a disturbance in the renal circulation. Active vasoconstriction, that is at least partially reversible, not affected by renal denervation and localized preponderantly in the efferent arteriole, is apparently the basis for structural alterations. Reduction in renal plasma flow without a change in glomerular filtration rate is a distinctive feature and often serves to differentiate the disorder from other entities causing hypertension in which filtration may be greatly reduced, such as chronic diffuse glomerulonephritis¹⁰⁵ and chronic pyelonephritis.¹⁰⁶

A similar functional pattern has been observed in the presence of hypertension caused by coarctation of the aorta.¹⁰⁷

ABDOMINAL VISCERA IN ESSENTIAL HYPERTENSION

The abdominal viscera are not disturbed by the processes of essential hypertension. Gastrointestinal disorders are relatively uncommon. Liver function is normal throughout the course of the disease although jaundice and other manifestations of hepatic dysfunction may occur independently or as a result of congestive heart failure. This apparent immunity of the splanchnic circuit is more astonishing when one considers its place in the total circulation. Measurements of hepatic venous outflow (or total splanchnic blood flow) by a method based on the measurement of hepatic bromsulphalein clearance indicates that one to two liters of blood, a large fraction of the cardiac output, leave the splanchnic bed each minute in normal persons.¹⁰⁸ Estimation of hepatic blood flow in patients with essential hypertension has shown no significant deviation from normal.^{109,110} This can mean only that vasoconstriction is present, probably affecting the hepatic and mesenteric arterioles. Since there is no evidence of an abnormality in portal venous pressure, it may be presumed that the process does not extend into the post-arteriolar vessels. Wilkins and his co-workers¹¹⁰ claim that splanchnic vasoconstriction is released by lumbodorsal sympathectomy because hepatic blood flow may increase markedly when resting blood pressure is not lowered. Hepatic flow changes little or not at all when blood pressure is lowered by the operation. Thus it appears that the splanchnic circuit participates in the generalized vasoconstriction, without incurring the damaging lesions that appear in the brain and kidney, although arteriolosclerosis may be widespread in the liver and pancreas.

MUSCLES AND SKIN IN ESSENTIAL HYPERTENSION

Disorders of the muscles and skin occur no more frequently among hypertensives

than among the population at large. A florid, ruddy complexion has often been considered a distinguishing characteristic although it apparently has little significance, if indeed it is at all connected with the disease. Some hypertensives complain of cold, clammy extremities, but quantitative studies of the water loss from the surface of the finger tips have shown no difference between hypertensives and normal subjects.¹¹¹ The skin temperature also falls within normal limits.¹¹² Thus, there is no evidence of altered circulation or abnormal sympathetic activity in the skin.

The blood flow through the extremities, which may be considered for practical purposes made up solely of skin and muscle, is normal in hypertensives, according to most studies,¹¹³⁻¹¹⁶ indicating an increased resistance to flow approximately proportional to the increment in arterial pressure. Since blood flow increases during warming to the same extent as in the normal, the increased resistance is considered to be vasoconstrictive rather than structural in origin, and apparently is not mediated by the autonomic system since sympathetic vasodilatation under these circumstances would be expected to cause excessive flow. A more effective method of inducing vasodilatation has been employed by Wilkins and Eichna.¹¹⁶ Vascular occlusion for a period of five minutes elicits what appears to be a constant maximal dilatation, and blood flow increases markedly (reactive hyperemia) in proportion to the existing level of blood pressure. Thus elevated arterial pressure due to hypertensive disease causes an enhanced blood flow during reactive hyperemia corresponding to that observed in normal persons in whom blood pressure has been increased to the same level with paredrinol. Sympathectomy of the limb does not alter this response. The fall of pressure following lumbodorsal sympathectomy is attended by a proportionate decrease in hyperemia flow. Wilkins and Eichna found that hyperemia flow returned to the preoperative level several months postoperatively in some patients, despite

continued normal blood pressure. This phenomenon may indicate slow relaxation or dilatation of constricted arterioles after return of the blood pressure to normal. Since the method of measurement is so unreliable, the range of normal variation so wide and the appearance of spontaneous variations in flow so common, these workers regarded the evidence as insufficient to prove that excessive vasoconstriction occurs in the peripheral vascular bed.

* * * * *

From a physiologic standpoint, essential hypertension is a vascular disease characterized by generalized arteriolar vasoconstriction which results in a sustained elevation in arterial pressure. It is possible that smooth muscle in the arteries and veins also undergoes contraction but evidence of this is scanty and inconclusive. In many cases the arterioles of the kidney and possibly the brain are involved to a greater extent than arterioles elsewhere in the body. Possibly because of such excessive constriction the vasculature and tissues of these organs suffer pathologic changes that are equalled or exceeded only in the heart. Cardiac damage is probably related to the burden of maintaining a normal flow of blood through the body against an augmented peripheral resistance.

Both the kidney and the nervous system have been implicated as possible primary sites of involvement. The chronologic relationship of vascular disturbances in these organs to the onset of hypertension has not been carefully defined although apparently hypertension can develop in the absence of any selective change.

Cortical, neural, humoral and local reflex vasomotor activity all contribute in shaping the complex physiologic manifestations of the disease. Too little is known to assign preëminence to any one factor in this process.

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Diagnosis and Natural History of Hypertensive Vascular Disease*

GEORGE A. PERERA, M.D.

New York, New York

IN considering the diagnosis and natural history of hypertensive vascular disease (HVD), it is essential that there be a common understanding as to the definition of this disorder. To achieve such an understanding is more difficult than might be supposed.

Ordinarily HVD is considered to be characterized by the presence of hypertension secondary to increased peripheral resistance in the arteriolar bed, other known causes of hypertension being absent. Hypertension is defined as an abnormal elevation of diastolic blood pressure. However, the normal blood pressure is determined by the composite interaction of many forces, and it is often impossible to make a sharp distinction between normal and abnormal values. Moreover, there may be periods in the course of HVD in which the blood pressure is not elevated. It must also be stressed that the rise in diastolic blood pressure, the criterion on which clinical diagnosis usually depends, represents an effect rather than a cause and is but one manifestation of the disorder.

These remarks serve to emphasize that definitions cannot be readily made until mechanisms are more clearly understood. There is no measurement more variable than that obtained by the determination of arterial tension. A discussion of the diagnosis and natural history of HVD properly begins, therefore, with an appreciation of the forces which influence the blood pressure.

NORMAL BLOOD PRESSURE^{1,2,3}

The maintenance of arterial pressure is dependent upon the output of the heart per

unit time and upon the blood volume, viscosity of the blood, elasticity of the larger arterial walls and the peripheral resistance offered primarily by the arterioles. These in turn may be modified by secondary regulatory mechanisms such as central and peripheral autonomic controls. The blood pressure exhibits innumerable fluctuations in which age, position, activity, obesity and particularly emotional state play an important part.

In this clinic normal "resting" blood pressure values, the lowest readings obtained on repeated examination by the same observer in a coöperative and relaxed subject lying in bed, are rarely above 120/80 mm. of mercury. Levels casually obtained are generally below 140/90. The blood pressure of children is lower than that of adults. Obesity may produce falsely high sphygmomanometric readings. Values in the 90/50 mm. range are not rare, particularly in young, asthenic individuals; in the absence of other causes of hypotension such levels should be looked upon as a constitutional variant and not as due to disease.

Once maturity is reached, the blood pressure does not increase with age except as a reflection of an underlying organic change, such as arteriosclerosis of the aorta with loss of vascular elasticity. The resultant systolic hypertension, which may also be found in some patients with hyperthyroidism, aortic insufficiency or heart block when the rate is slow, should be sharply separated from those conditions in which there is elevation of the diastolic blood pressure.

The blood pressure is slightly influenced by respiration and position. Profound in-

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y. This study was made possible through the generosity of the Albert and Mary Lasker Foundation, and in part by a grant provided by the National Institute of Health (U.S.P.H.S.).

creases in systolic pressure may accompany exercise. Emotional influences exert marked effects, particularly upon the systolic pressure. Some hyperreactive individuals, often with autonomic nervous system imbalance, may exhibit occasional and transient abnormal elevations of blood pressure as high as 160/100 mm. of mercury and may show this tendency for transitory hypertension for months or a lifetime. Changes as great as 50 mm. of mercury systolic and 20 mm. of mercury diastolic can occur in less than one minute or two.

The arterial pressure may be further affected by underlying pathologic states unrelated to specific causes of hypertension. These include cardiac arrhythmias, arteriovenous communications, pain, fever, shock and hypofunction of the thyroid, adrenal or pituitary glands.

Unless the conditions of measurement are accurately determined and constantly maintained, analyses of normal blood pressure readings are without significance. It is more important to realize that there is a wide and variable range in normal blood pressure.

HYPERTENSION^{4,5,6}

From the preceding remarks it is obvious that an overlap exists which makes a sharp differentiation between normotension and hypertension impossible. Hypertension should be suspected only if the diastolic blood pressure occasionally rises above 90 mm. of mercury. It becomes increasingly probable the more often this value is exceeded. Lability of blood pressure readings is characteristic of the early hypertensive state, is sometimes observed throughout its course and should be regarded as a true manifestation of the disorder.

The systolic blood pressure is usually increased in hypertension, but a reading of less than 140 mm. of mercury does not exclude the hypertensive state, nor does a normal blood pressure always exclude antecedent hypertension. Many hypertensive subjects have been observed in this clinic with a reduction in tension to normal or even low normal values following rest or

relaxation. Periods up to three weeks are often required before minimal readings are obtained. "Resting" values in one patient (with retinitis, cardiac hypertrophy and repeated casual blood pressure determinations never recorded below 170/100 mm. of mercury) fell as low as 90/52 on hospital admission and rose promptly to original values upon discharge. Fever frequently lowers the blood pressure for days. Normotension may persist for many months after a hypertensive subject has developed a myocardial infarction or cerebral vascular accident.

DIAGNOSIS

The diagnosis of HVD rests at present on the repeated finding of hypertension when other causes of diastolic blood pressure elevation are excluded. As previously pointed out, there are obvious difficulties in many cases in deciding whether or not hypertension exists. In the absence of consistent and significant deviations from normal, time and hindsight may be required before conclusions can be reached.

Many congenital and acquired primary disorders of the urinary tract or renal circulation, particularly acute and chronic glomerulonephritis, polycystic kidneys, pyelonephritis and urinary tract obstruction, may be associated with hypertension. Other disease processes include coarctation of the aorta, hypertension in toxemia of pregnancy, adrenal and pituitary tumors, pheochromocytomata, lupus erythematosus disseminatus and periarteritis nodosa. A complete list would include many other conditions, ranging from acute hypertension of central nervous origin to carbon tetrachloride poisoning and acute porphyria, but the above comprise the more frequent disorders involved in differential diagnosis.

INCIDENCE

Mortality statistics deal with cardiovascular and renal deaths, not with hypertension alone. Hospital, industrial, military, insurance and other figures are often difficult to interpret because of varying criteria

of diagnosis, predominance of selected groups in different series, casual or single blood pressure determinations and inadequate documentation.

Among 2,000 unselected and apparently healthy men between the ages of twenty to thirty we have found repeated "resting" blood pressures consistently above 140/90 mm. of mercury in thirty-four subjects (1.7 per cent), all of whom had several negative urinalyses. In examining Robinson and Bruce's unselected group,⁷ it may be noted that of 2,387 males and 1,178 females between the ages of thirty to forty, approximately 4 per cent showed diastolic values in excess of 90 mm. of mercury in the course of one thirty-minute period of observation. In a series of 10,883 persons in all age groups, about 7 per cent exhibited abnormal diastolic readings. Several series report a much higher incidence, but systolic hypertension or possible labile blood pressures are rarely excluded from consideration.

In all probability the true incidence of hypertension lies between these extreme values, certainly not less than 2 per cent and probably not more than 7 per cent. It would be reasonable to assume that about 5 per cent of the adult population of the United States is afflicted with this disorder.*

HVD is said to be less evident among primitive peoples unless they are transferred to more civilized environments. Heredity is an important factor, with the majority of surveys indicating a clear-cut family history in 50 to 60 per cent. Obesity, short and stocky body types and hyperkinetic bodily reactions appear to be present more frequently in association with hypertension. Psychological types have been repeatedly described, a large percentage of subjects showing hostility and aggressive conflicts, emotional lability and anxiety patterns expressed in acute generalized reactions

rather than localized or referred. "Abnormal vascular responsiveness," "hyperreactivity," and the "prehypertensive state" are terms frequently encountered. Although normotensives whose vasomotor patterns react in excess are statistically more likely to develop hypertension, hyperreactivity is not an infallible warning.

It is generally agreed that HVD is somewhat more common among women. However, it is difficult to arrive at exact ratios, as the hypertensive state is frequently recognized for the first time during pregnancy. If one chooses to group persistent post-toxemia and postpartum elevations of blood pressure with prepregnant hypertension, this disorder is about four times as common in women as in men. If one excludes all female subjects in whom the onset of hypertension and pregnancy appear to be related, a 2 to 1 or even smaller ratio results.

NATURAL HISTORY OF THE DISEASE

For reasons that have been stated elsewhere,⁸ an accurate and complete picture of the natural history of HVD is not readily achieved. Varying diagnostic criteria and difficulties in obtaining an unselected series have made many reports open to criticism. There are many obstacles which prevent documentation of the disease from its incipency, as the majority of patients seek care only after symptoms appear.

To avoid selection as much as possible, data have been secured from multiple sources. Records of 2,147 patients with established HVD were obtained from a hypertensive clinic which has operated continuously for more than twenty years, from hospital admissions, hospital personnel, student health, private practice and industrial sources. From these it was possible to select 250 subjects followed at frequent enough intervals for more detailed analysis, none of whom had received therapy other than reassurance or mild sedation. The basis of selection consisted only in the documentation of HVD (repeated diastolic blood pressure values above 90 mm. of mercury, and the exclusion of other causes of hyperten-

* Although it is common practice to record the incidence of HVD as about 25 per cent, the conclusion expressed is based on the argument that the disorder starts earlier than is generally assumed, and that the hypertension observed in older age groups includes many subjects with systolic hypertension or degenerative vascular disease. This remains a controversial subject.

sion) and a sufficient period of observation to permit complete routine studies and the elimination of subjects whose hypertension was transient. Even so, some element of selection is inherent in a study of this kind. The group of 250 patients represented

siderable additional information must be gathered before a complete understanding of the natural history of the disorder is obtained.

Age at Onset. A few authors^{7,9,10} have suggested that HVD begins at an early age.

TABLE I
SUMMARIZED DATA IN STUDY OF HYPERTENSIVE VASCULAR DISEASE

Total number of patients with HVD whose records were examined	2,147
Men	795
Women	1,352
Rapidly progressive or malignant hypertension	103
Total number of patients with HVD analyzed in greater detail	250
Men	85
Women	165
Living at the time the survey was made	207
Dead at the time the survey was made	43
Average age at time of diagnosis	36 years (range 15-67)
Average period of observation	12 years (range 2-41)
Average blood pressure at time of diagnosis	182/108 mm Hg
Average blood pressure at time of last observation (excluding critically ill or terminal cases)	202/116 mm Hg
Symptoms and signs observed in series of 250 cases*	
No symptoms during period of observation	14
Headaches	78
Migraine headaches	3
Retinal arteriolar irregularity or arteriovenous compression	94
Hemorrhages, exudate or papilledema	19
Hypertensive encephalopathy	2
Abnormalities of urine or renal function	35
Nitrogen retention	5
Increased cardiac area by x-ray	71
Electrocardiographic changes	86
Electrocardiographic changes indicative of myocardial damage	38
Cardiac pain	18
Myocardial infarction	9
Congestive failure	40
Cerebral vascular accidents	12

* Expressed in per cent of 250 cases

primarily a clinic and hospital population; subjects who appeared for the first time with a terminal episode were obviously not included; the duration of hypertension prior to the first observation was inevitably unknown.

Hence these data, summarized in Table I, permit only general conclusions and con-

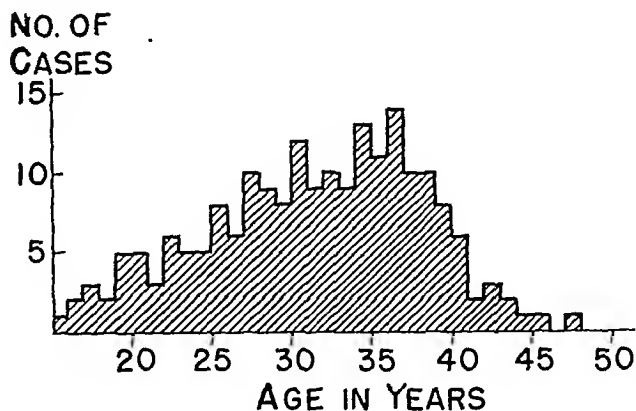


Fig 1 Age of 200 subjects at onset of hypertension

This is in contrast to the general acceptance of the view that the disorder is primarily "a disease of the declining years."⁶ The present study supports the contention that HVD usually becomes apparent in youth and early adult life.

It was possible to establish the age at onset of hypertension in 200 subjects by the documentation of HVD and its sequelae following a period of known normal blood pressure. Normotensive criteria included multiple normal blood pressure determinations in individuals not on bed rest or in the hospital and not obtained during convalescence from acute or febrile illness. Hypertensive criteria included multiple readings greater than 140/90 mm. of mercury, at least three negative urinalyses, no clinical evidence of other causes of hypertension and onset not in association with pregnancy. All subjects were followed for at least two years, with ultimate development of at least one objective hypertensive complication. The series was obtained by examination of the 2,147 hypertensive records mentioned above, all of individuals at least seventeen years of age at the time of final observation, 50 per cent over the age of forty, and 17 per cent ranging in age from

fifty-five to eighty-six. The age at which hypertension was first manifest was recorded even though the last normotensive observation frequently preceded this point by periods as long as five years.

The data (Fig. 1) indicate that the onset of hypertension invariably occurred in subjects under forty-eight years of age, all but sixteen (92 per cent) being under the age of forty. The failure to demonstrate the appearance of hypertension in older subjects in no way excludes the possibility that it may occur at any age.

Sex. There were 1,352 women and 795 men in the entire series, a 3 to 2 ratio favoring women.

Duration of Life. The average period of observation in the group of 250 patients studied in detail was twelve years. In the selected series in which the onset of HVD could be documented the average period of observation was fifteen years. Long survival (more than twenty years), often with comparative well being, was not a rarity. One woman, still in reasonably good health, had had definitely established and repeatedly recorded hypertension for more than forty-one years.

It is well established that HVD and its sequelae reduce life expectancy and may cause death within a period of months from the time of diagnosis, but a survey of the 2,147 hypertensive records indicated that in only 5 per cent could the diagnosis of malignant hypertension be entertained. As the majority of records studied indicated well established disease when first seen, and as the majority are still living, it must be emphasized that average life expectancy is undoubtedly longer than generally assumed and, if anything, longer than these figures would indicate.

Symptoms. HVD may be present for many years without symptoms. The majority (86 per cent) of patients complained of fatigue, weakness, nervousness, dizziness, palpitation, insomnia or headaches at some time in the course of their disease. Evidence of autonomic instability was not infrequent. It must be recalled, however, that some of

these symptoms are not uncommon in the general population.

Headaches (78 per cent*) were usually of minor degree and even the more intense headaches were inconstant and often disappeared completely after months or years of great severity. They were usually occipital, generalized or over the vertex, more apt to be present on awakening or in the morning and on occasion (3 per cent) assumed a typical migraine pattern in subjects with no familial or previous history of idiopathic migraine. The frequency of headaches as a complaint in normotensive individuals and occasional encounters with headaches due to other causes, make it advisable to consider other etiologies rather than to attribute them routinely to the hypertensive state.

Blood pressure: Although there was considerable variation in individual cases, the general tendency of the blood pressure was to increase but slowly throughout the years of observation.

Retinopathy: Retinal abnormalities were common in the group of 250 patients studied, and eventually included arteriolar irregularities and arteriovenous compression (94 per cent), hemorrhages, exudate or papilledema (19 per cent). In rare cases even severe retinitis showed conspicuous regression. Intermittent spasm of retinal vessels could sometimes be seen on ophthalmoscopic examination. It was found wholly impractical to classify hypertension according to the degree of retinitis; even malignant hypertension could appear without significant retinal change.

Hypertensive Encephalopathy. In patients with marked hypertension or in the rapidly progressive malignant phase of their disease, acute recurrent attacks of convulsions, headaches, vomiting, mental changes, transitory paralyses and the like may occur (2 per cent).

Arteriolar Nephrosclerosis. In the series studied, about one-third of the hypertensive group eventually exhibited some renal

* Percentage figures refer to the 250 hypertensives in whom detailed analyses were possible.

abnormalities in the form of relative polyuria, nocturia, diminished concentration power and albuminuria, with or without the presence of urinary red cells and casts. Tests indicating progressive glomerular and tubular damage accompanied these findings. Nitrogen retention developed in 5 per cent.

It must be kept in mind that not all the renal findings need be on the basis of arteriolar nephrosclerosis alone. At times renal arteriosclerosis may contribute to the picture, and reduced renal blood flow secondary to congestive failure may be an additive factor.

Hypertensive Heart Disease. Evidence of an increased cardiac area by x-ray (primarily enlargement of the left ventricle) was obtained in 71 per cent. As compared with other pathologic changes in HVD, cardiac hypertrophy was conspicuously absent in some cases even after long-sustained hypertension. There is accumulating evidence that cardiac hypertrophy can scarcely be attributed only to the elevation of blood pressure, arteriosclerosis or to the work of the heart. Congestive failure may occur with no demonstrable coronary artery disease subsequently revealed at autopsy.

Accentuation of the second aortic sound, apical and aortic systolic murmurs and occasional split sounds were frequently recorded. Electrocardiographic changes consisting of left axis deviation and left ventricular strain patterns appeared in the majority of patients.

ARTERIOSCLEROTIC VASCULAR COMPLICATIONS

It may be debated as to whether degenerative alterations in arteries are augmented by the hypertensive state or are merely coincidental. The frequency of coronary artery disease, cerebral vascular accidents and peripheral vascular changes among hypertensives, as well as comparative analyses of autopsy material, favor the former interpretation. No consistent relationship of any of these complications to blood pressure levels or duration of the disorder could be established.

Coronary artery disease: Cardiac pain was a complaint in 18 per cent of the patients at some time during their course. Myocardial infarction occurred in 9 per cent and electrocardiographic changes indicative of myocardial damage developed in 38 per cent. Manifestations of congestive failure appeared in 40 per cent, but it must be recalled that hypertrophy alone, as well as coronary artery disease, may be associated with failure.

Cerebral vascular accidents occurred in 12 per cent of the patients in this series, often in the form of hemorrhage resulting in death, but at times in the form of multiple thrombotic episodes.

In addition to cerebral hemorrhage, epistaxes and menorrhagia are not uncommon in hypertension, and subcutaneous, pulmonary, subarachnoid, gastrointestinal, renal and adrenal hemorrhages have been reported.

MALIGNANT HYPERTENSION

This term is applicable to rapidly progressive HVD and is associated with necrosis of the arteriolar walls, advanced hyalinization and petechial hemorrhages superimposed upon the arteriosclerotic picture, involving particularly the kidneys and retinae. Although malignant hypertension was on occasion apparent at the onset, it was more apt to develop without warning among patients who previously exhibited a mild and static course. The majority exhibiting this phase were males. The diagnosis of malignant hypertension appeared probable in 5 per cent of the over-all series of 2,147 patients.

PROGNOSIS

In analyzing this series, nothing appeared to alter the impression gained in the study of a selected group.⁸ In general, the initial height of blood pressure, headaches and other symptoms, cardiac hypertrophy and retinal changes without retinitis bore no relationship to ultimate outlook. Progressive rise in blood pressure, cerebral vascular accidents, retinitis, coronary artery disease,

congestive failure or albuminuria indicated a relatively poor prognosis though with notable individual exceptions.

CAUSE OF DEATH

Death in HVD is due chiefly to arteriosclerotic complications. The data in this series are too few to be significant, but figures from the literature indicate that congestive failure (40 to 50 per cent), myocardial infarction and cerebral hemorrhage (each 10 to 20 per cent) are leading causes with not more than 5 per cent dying of renal insufficiency.

CONCLUSIONS

Measurement of the blood pressure is at best rough and variable. A sharp differentiation between normotension and hypertension is impossible. Although high blood pressure is but a manifestation of HVD, the clinical diagnosis rests on the repeated finding of hypertension when other causes of diastolic blood pressure elevation are excluded. It should be emphasized that systolic hypertension alone must be separated from those disorders in which the diastolic blood pressure is affected, and that a normal blood pressure may be recorded in the course of HVD under certain physiologic and pathologic conditions.

HVD is a common disorder, the first signs of which usually appear in youth and early adult life. The course of HVD is extremely variable, with gradations from a benign, asymptomatic form to cases of malignant hypertension with a rapidly fatal outcome.

Average life expectancy is, however, considerably longer than is generally assumed.

The symptoms, signs, complications and outlook are dependent upon associated autonomic instability, arteriolosclerosis, hypertensive heart disease, and arteriosclerotic changes. These alterations are frequently but not invariably present, differ in their intensity and points of maximal attack and are not related to the level of the blood pressure or to the duration of the disease.

Considerable additional data must be gathered before complete information concerning the natural history of HVD is obtained.

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Conference on Therapy

Treatment of Pneumonia

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. WALSH McDERMOTT: This conference will be on the management of pneumonia. The discussion will be opened by Dr. Tompsett.

DR. RALPH TOMPSETT: The therapeutic aims in the treatment of pneumonia are: first, to control the infection, second, to promote the patient's comfort and third, to manage or, if possible, prevent the development of irreversible anatomic or physiologic changes during the period required for the control of the infection. Accomplishment of these aims requires the use of specific antimicrobial agents chosen on the basis of the etiology of the disease in the particular patient and certain general measures which are useful in pneumonia regardless of etiology. In no case may either the specific or the general measures be neglected. The need for many of the general measures, however, is considerably reduced in those forms of pneumonia for which potent antimicrobial agents are available.

The most successful use of penicillin, streptomycin and sulfonamides in pneumonia requires accurate bacteriologic diagnosis. Consideration of the present situation, however, makes it quite evident that the physician must do a great deal of work to discover a relatively few patients for whom potent antimicrobial agents other than penicillin are available. As you know, probably over 95 per cent of all the patients with primary pneumonia will be found either to have pneumococcal pneumonia or primary atypical pneumonia. If penicillin is given to all of these patients purely on the basis of the diagnosis of pneumonia without

regard to etiology, most of the patients will be receiving as effective an antimicrobial agent as is available. Some of them who have primary atypical pneumonia, will not be helped by the drug but very little, if any, harm will be done.

Thus, efforts made to arrive at a precise bacteriologic diagnosis are directed toward the detection of a relatively small number of cases, the most important of which are those caused by Friedländer's bacillus and tubercle bacillus. It is important that these cases be detected early because the serious damage which may occur within a short time may often be prevented by correct therapy.

In pneumococcal pneumonia, the commonest form of pneumonia aside from those occurring in epidemics, the most effective agent for the control of the infection is penicillin. The dosage of penicillin generally employed is approximately 20,000 units dissolved in 1 cc. of saline solution, given intramuscularly every three hours. Larger doses may be used if it is desired to lengthen the interval between injections. Equally satisfactory results may be obtained by the use of penicillin orally in doses of 100,000 units every two hours.

A variety of vehicles have been proposed for the administration of penicillin in an attempt to delay its absorption and thus obviate the necessity for repeated injections. One preparation, the "Romansky formula" of penicillin in oil and beeswax, has received extensive clinical trial. With this preparation it is possible to treat patients with pneumococcal pneumonia using only one

or two daily injections of 300,000 units of penicillin. Recently liquid preparations of this material have become available and these have done away with some of the disadvantages of the earlier preparations.

Therapy of pneumococcal pneumonia by any of these regimens should be continued for a minimum of seven days and preferably for ten days. With this treatment many patients with pneumococcal pneumonia may be expected to have a crisis within twenty-four hours, and in the vast majority within forty-eight hours. In the remainder of the uncomplicated cases by the end of the forty-eight-hour period there will be definite evidence of improvement but the defervescence may be less abrupt. In some, after this initial period of defervescence, there follows a period of secondary low grade daily fever which may persist for as long as a week, although not accompanied by other evidence of toxemia. Failure to obtain a response to penicillin therapy in the form of one or another of the patterns which I have described constitutes strong evidence that some complication is present, or that the pneumonia is not caused by pneumococcus.

The various methods of administration of penicillin I have mentioned have been notably satisfactory in pneumonia. All of them involve an attempt to maintain "continuously effective" antimicrobial concentrations of penicillin in the body which experience has shown are very effective. It has also been shown that it is not necessary to maintain continuously high concentrations. The studies of Tillett and his associates have shown that satisfactory results may be obtained in the treatment of pneumococcal pneumonia with the use of doses of only 10,000 to 25,000 units of penicillin in saline, given three or four times a day. It was further shown by these workers that equally satisfactory results were obtained when some of the intervals between doses were twelve to sixteen hours. Other clinical studies have shown satisfactory results with dosage regimens which could not possibly have maintained what

were previously considered "therapeutic levels" for more than twelve to fifteen hours in each day. During the past seven months we have treated twenty-six patients with pneumococcal pneumonia, employing injections of aqueous solutions of penicillin, 300,000 units each, at intervals of twelve to twenty-four hours. It has been our practice to give a dose of 300,000 units as soon as the diagnosis is made. Then the patient is given 300,000 units at 8:00 A.M. and 8:00 P.M. until it is seen that defervescence is occurring. At this point, the regimen is changed to only one injection of 300,000 units a day, at 8:00 A.M. The results in these twenty-six patients, as judged by all the usual criteria, have been identical with those of other treatment regimens.

There are two other forms of pneumonia in which the same principles of penicillin therapy are applicable. These are streptococcal and staphylococcal pneumonia. It is possible that streptococcal pneumonia occurs fairly frequently in a mild form following pharyngitis and, if so, it closely resembles atypical pneumonia. This is not the same entity as the well known streptococcal pneumonia in which there is a widespread involvement of the lung, with all the manifestations of a severe infection and rapid development of empyema, bacteremia and metastatic abscesses. It appears that satisfactory results may be anticipated in this severe form of streptococcal pneumonia with the use of penicillin, provided therapy is instituted early enough and before irreversible anatomic or physiologic changes have occurred. In these cases it may be well to use the agent in dosage two or three times as high as that used in pneumococcal pneumonia.

Staphylococcal pneumonia is also rare. Most of the experience has been gained in those cases which occur in association with epidemics of influenza. The same general principles apply as with streptococcal pneumonia. The penicillin dosage should be even larger for, although many strains of staphylococci are highly sensitive to penicillin, there is considerable variation among freshly

isolated strains. Virtually all cases, however, may be expected to be favorably influenced by large doses of penicillin.

The second most frequent type among the bacterial pneumonias is that caused by Friedländer's bacillus. Although these cases make up only a small proportion of all the pneumonias, they constitute a particularly important group today because they are not influenced by penicillin, whereas they respond favorably to streptomycin and the sulfonamides. The recognition of cases of Friedländer's pneumonia is made even more important by the fact that all too frequently their progression is rapid; within a day or two of the time the patient presents himself to the physician, the stage of abscess formation is reached. Experience with Friedländer's pneumonia indicates that the treatment of choice is the combined use of streptomycin and a sulfonamide. The organisms are generally sensitive to streptomycin. Many of the strains are also susceptible to sulfonamides. Despite the fact that in many of the patients treated with streptomycin alone the results have been satisfactory, there is theoretical reason, supported by many *in vitro* studies, to believe that the combined use of the two drugs may prevent or postpone the emergence of organisms resistant to streptomycin. The average dose of streptomycin is 40 mg. per Kg. daily or about 2.0 Gm. per day in the average patient, given in three or four fractions by intramuscular injection. The usual dose of the sulfonamides is used; for example, 2 Gm. of sulfadiazine as the initial oral dose, followed by 1 Gm. every four hours.

Another form of pneumonia which may be of acute onset and which may very closely simulate the more usual varieties is tuberculous pneumonia. This may also progress rapidly to the stage of irreversible or incompletely reversible damage. Consequently, early recognition of the etiology is of the utmost importance. Here also, early use of streptomycin offers the best possibility for reversal of the inflammatory process. The daily dosage of streptomycin is somewhat smaller than in the case of Friedländer's

infection because the treatment is more prolonged.

The general measures, namely, those of keeping the patient at rest during the acute phase of the pneumonia, relief of pain with codeine or morphine and the use of oxygen therapy may all be necessary. They have less importance in those cases in which effective antimicrobial agents are available. In some cases, such as the primary atypical pneumonias, they may be the only type of therapy available. Such supportive measures are very helpful in these cases, as well as in other forms of pneumonia with complications and in those who come under medical care only after the disease is in the advanced stage.

DR. McDERMOTT: As Dr. Tompsett said, the two important features in the management of pneumonia are the proper use of antimicrobial therapy and the institution of the general measures mentioned. In most patients with bacterial pneumonia these general "supportive measures" are no longer of great importance. In the other large group of pneumonias, identified by the clinical syndrome of primary atypical pneumonia, the general measures may be of prime importance since no antimicrobial therapy is available.

We are fortunate today in having with us Dr. Frank Horsfall and Dr. Harold Ginsberg of the Rockefeller Institute. We promised that we would not call on them for any formal presentation but they are available for questions. I might start by asking them some questions on atypical pneumonia. As you know, however, these gentlemen have not limited their studies to atypical pneumonia and we may take advantage of their presence by questions on other aspects of pneumonia as well.

Dr. Horsfall, I would like to ask you about a question which is repeatedly discussed on the service: Can one be sufficiently certain of the diagnosis of the clinical syndrome of primary atypical pneumonia to justify withholding antimicrobial therapy for, let us say, a forty-eight-hour period, or should all patients with an acute pneumonia receive

antimicrobial therapy for a trial period with the view in mind that the response will help to establish the diagnosis of atypical pneumonia?

DR. FRANK HORSFALL: It would seem to me that in the large majority of patients with primary atypical pneumonia a careful clinical examination, including a white blood cell count, ought to make it possible to conclude that the disease is probably not bacterial pneumonia. There is a fairly sharp difference between the majority of patients with primary atypical pneumonia and the majority of patients with bacterial pneumonia. Physicians who are accustomed to seeing pneumonia should, in the majority of instances, have no great difficulty in differentiating one from the other.

As to the second half of your question, if one is reasonably sure that the diagnosis is primary atypical pneumonia, it seems to me not only unnecessary but indeed unwise and poor medicine to give a therapeutic agent which has no effect on the disease merely for the purposes of security.

DR. HARRY GOLD: Would Dr. Tompsett state how he makes fairly certain that the pneumonia is the primary atypical variety? What are its diagnostic characteristics, and especially the decisive ones?

DR. TOMPSETT: One can be fairly certain of the diagnosis of primary atypical pneumonia only by careful evaluation of several features of the disease in comparison with similar features of bacterial pneumonia. In primary atypical pneumonia, the onset is generally less acute and the symptoms are less severe than at the same stage of bacterial pneumonia. Chest pain is less likely to be prominent. The cough may be distressing but is often not productive of much sputum and the sputum is not likely to be bloody or rusty in the early stages. The white blood cell count is generally between 5,000 and 10,000 per mm.³ and although it may be higher, it rarely goes as high as one generally finds it in the bacterial pneumonias. Those are the chief features. It should be emphasized, in connection with the white cell count, that patients with very severe bac-

terial pneumonia may not have a leukocytosis and may even have counts below 5,000. These cases, however, are not the ones in which confusion arises.

DR. McDERMOTT: The notion has been advanced that the administration of antimicrobial therapy might prevent a so-called secondary infection in these patients. Has secondary infection been a problem in primary atypical pneumonia?

DR. HORSFALL: Secondary infections in primary atypical pneumonia are exceedingly rare. Their incidence is certainly not greater than 1 in 200. When they occur, they can be recognized at once and that is not too late for successful antibacterial therapy. To give 199 patients frequent injections in the hope of preventing bacterial infection in one, seems to me unnecessary and overzealous treatment.

DR. McDERMOTT: I have never seen bacterial infections following the atypical pneumonias we encounter here.

DR. HORSFALL: It does happen but it is rare.

DR. McDERMOTT: Dr. Tompsett said something about mild forms of bacterial pneumonia, such as streptococcal pneumonia with which we are all familiar. Such cases might resemble atypical pneumonia. Have you any thoughts on that point?

DR. HORSFALL: I agree with what Dr. Tompsett has said and, indeed, I will go one step further. We have seen patients in whom we did not suspect bacterial pneumonia but who, on careful study, proved to have had pneumococcal pneumonia. The clinical findings, the x-ray and even the leukocyte count strongly suggested that the infection was primary atypical pneumonia. Finally, when all the serologic and other laboratory work was completed, it became evident that it was not the correct diagnosis, and that the patient actually had pneumococcal pneumonia due to a specific type of pneumococcus and showed a specific antibody response. But this is a rare occurrence and such cases do not constitute a therapeutic problem because they are so mild.

DR. McDERMOTT: That brings up another problem. It is virtually impossible now to obtain diagnostic sera for the typing of pneumococci in sputum. What do you think about the necessity or the clinical usefulness of typing sputum?

DR. HORSFALL: That is an exceedingly difficult question to answer and particularly difficult for me. It would seem to me that there is little clinical usefulness in typing pneumococci at the present time. Indeed, some of the best clinics in this city, and in others, carry out very effective therapeutic regimens in pneumococcal pneumonia and unfortunately have no idea with what types they are dealing. Manifestly, one can, if necessary, handle the therapy of pneumococcal pneumonia satisfactorily without knowing the type.

DR. McDERMOTT: I agree, but I believe that typing is still of very great importance. To be sure, pneumococcal pneumonias can be treated successfully without diagnosis of the type. But there remains the small number of bacterial pneumonias which require specific antibacterial agents not used in pneumococcal pneumonia. It is, therefore, essential to establish the diagnosis of pneumococcal pneumonia and typing seems to me the quickest way of recognizing that group. If one finds a Type I or Type II, or if one is able to recognize the pneumococcus by direct typing, it is fairly convincing evidence that the patient has pneumococcal pneumonia and not one of the other bacterial pneumonias. Would you agree to that?

DR. HORSFALL: No, not entirely.

DR. McDERMOTT: You would not?

DR. HORSFALL: Unfortunately, no. I agree with most of what you have stated regarding the advantages of typing. But it seems to me that to make a diagnosis of pneumococcal pneumonia, one must have more evidence than the fact that a certain type of pneumococcus is present in the sputum. If it turns out to be Type I or Type II, I agree that the evidence is fairly decisive; but if the higher types, including III, V, VII, VIII, XIV and others are discovered, it

is uncertain that the pneumonia is due to the pneumococcus.

DR. McDERMOTT: I would agree that the higher types leave one uncertain. Would you agree that direct typing is a quick means of establishing the fact that pneumococci are present in the sputum? The interpretation of the finding in relation to the etiology of the disease is, to be sure, another matter. Direct typing of sputum at least shows pneumococci are there and might possibly be the cause of pneumonia.

DR. HORSFALL: I would agree to that.

DR. McDERMOTT: Dr. Ginsberg, how long should patients with atypical pneumonia remain in bed? We have seen relapses and we were quite impressed with the studies during the war which indicated that relapses were frequent when the patients were allowed up too early.

DR. HAROLD GINSBERG: The general criteria which have been set up in our own hospital and in others are as follows: The patient should not be up and about as long as there is fever or a fair number of crepitant râles. In a small number of patients a very few dry fine râles may be heard during the early part of convalescence which disappear faster if the patient is allowed some activity. I strongly believe that x-ray finding of consolidation should not alone be a factor in keeping a patient in bed.

DR. McDERMOTT: But they should be kept in bed if they have physical signs?

DR. GINSBERG: Yes, they should be when there are physical signs. We all know that patients may show areas of consolidation by x-ray which last as long as two or three months and sometimes longer. Those patients may be returned even to full activity. In the Army it was quite common to send such patients to reconditioning centers and allow them full activity there.

DR. McDERMOTT: With roentgenologic but no other evidence of pneumonia?

DR. GINSBERG: That is correct.

DR. McDERMOTT: But not with physical signs?

DR. GINSBERG: No, not with physical signs. In the separation centers it was a

common practice to have patients sent to the hospital because they showed x-ray signs, never having had a physical sign or symptom. Full activity has never been shown to be harmful in those patients.

DR. McDERMOTT: Do you believe that premature activity predisposes to relapse?

DR. GINSBERG: Yes, I do.

DR. McDERMOTT: Do you find the sedimentation rate of any value?

DR. GINSBERG: I think that often the sedimentation rate is down to normal while they still have abnormal physical signs and in that case I would not allow them unlimited activity.

DR. McDERMOTT: I take it that you allow these patients to be up and about when the fever has subsided even though they show rôles of a particular type? Have you any idea why they tend to relapse if you allow them unlimited activity too soon?

DR. GINSBERG: No. I am not even sure it is so although it seems to be. What do you think, Dr. Horsfall?

DR. HORSFALL: I do not know of any evidence which proves that they relapse more frequently when they are allowed up in the presence of physical signs. Nonetheless, it seems to me wise to keep them in bed when signs are present.

DR. McDERMOTT: Dr. Muschenheim, would you agree with Dr. Tompsett's statement that tuberculous pneumonia can mimic an acute bacterial pneumonia or the atypical pneumonia?

DR. CARL MUSCHENHEIM: I think it is much more likely to mimic atypical pneumonia than bacterial pneumonia, particularly because the white blood cell count is so frequently normal or only slightly elevated in both atypical pneumonia and tuberculous pneumonia. In fact, I think one of the most difficult differential diagnoses in pneumonia is that between primary atypical pneumonia and tuberculous pneumonia. As Dr. Tompsett has pointed out, this differential diagnosis is of increasing importance now that we have an effective treatment for tuberculous pneumonia.

DR. McDERMOTT: Perhaps you are not as apt to use chemotherapy in those tuberculous pneumonias which resemble atypical as in those which resemble the other bacterial forms. In other words, you might not want to give streptomycin immediately to a patient who had just a small patch of consolidation, whereas you probably would start streptomycin therapy at once in the patient with involvement of an area as large as two-thirds of a lobe or a whole lobe.

DR. MUSCHENHEIM: It is not uncommon in atypical pneumonia to have large areas of consolidation.

DR. McDERMOTT: In the extensive tuberculous pneumonias that involve most or all of a lobe with an acute exudative process, how difficult is it to demonstrate tubercle bacilli in the sputum?

DR. MUSCHENHEIM: Sometimes it is quite difficult. I think most failures are occasioned by not looking for them right away. Often the diagnosis is not even considered at first. They are frequently confused with the other bacterial pneumonias and the diagnosis is not thought of until there is a failure of response to penicillin or sulfonamide. Then, in other cases thought to be primary atypical pneumonia, tuberculosis is not considered until weeks have passed in which the presumed atypical pneumonia has failed to improve as anticipated.

DR. McDERMOTT: It should be possible then to demonstrate tubercle bacilli readily?

DR. MUSCHENHEIM: In the early stages one or two negative sputum examinations are sometimes obtained but one or two negative sputum examinations for acid-fast bacilli certainly do not even rule out the diagnosis.

DR. McDERMOTT: I do not wish to ask all the questions. Are there other questions now?

DR. McKEEN CATTELL: I have one for you, Dr. McDermott. A year or two ago you accumulated some pretty convincing evidence showing that the high peak concentrations are not important in relation to penicillin therapy. I am wondering whether

this new schedule of doses at twenty-four-hour intervals does violence to that idea?

DR. McDERMOTT: I think it is impossible to say, Dr. Cattell, because no one really knows whether or not the high peaks of penicillin concentration above a certain point serve a useful purpose. It is suspected that the high peaks do not serve a useful purpose. One of the main reasons for suspecting this is the notable efficacy of the penicillin-beeswax preparations in which peaks are seldom obtained. In evaluating the type of intermittent therapy we have employed one must consider two features of the penicillin concentrations: first, the intramuscular administration of 300,000 units of aqueous penicillin produces a very high concentration of penicillin in the circulating blood within a few minutes; second, it also results in the maintenance of penicillin concentrations above a certain minimum level for a fairly long period of time. We believe that the "effective concentration" of penicillin in the body is not known. It is generally assumed that in a particular infection there is a certain "effective concentration" of penicillin at the site of infection. Presumably, concentrations below this are ineffectual and increments above that value are of no added benefit. Obviously, for successful therapy in acute infections it is necessary to maintain "effective" antimicrobial action for some period during each twenty-four hours. The length of that period, whether it be four hours or twenty-four hours, probably depends on the speed with which that particular bacterial species multiplies and produces pathologic changes. Dr. Tillett's work, which has been amply confirmed by numerous investigators, would indicate that in pneumococcal pneumonia one has only to maintain the minimum detectable concentration of penicillin for about six hours out of the twenty-four and the regimen Dr. Tompsett has been using provides just about that by a single injection of 300,000 units of aqueous penicillin daily.

DR. CATTELL: What concentration do you regard as an effective one in pneumococcal pneumonia?

DR. McDERMOTT: We do not know. We suspect that it is less than the minimal detectable concentration which is approximately 0.08 units per cc. of serum with the method of assay we use. In staphylococcus infections the effective concentration is higher.

DR. GOLD: Do you regard a period of time below this presumed "effective concentration" in the blood as an important feature in therapy? That is to say, do you aim to supply the drug in such a way as to provide, first, a high peak, then a plateau of an "effective concentration" and finally, a period below an "effective concentration" as a means of making the organisms more amenable to reason?

DR. McDERMOTT: I do not think we can carry it quite that far, Dr. Gold. The original purpose of intermittent therapy was merely for convenience. There is evidence in one particular infection that one form of humoral immunity to the infection is much less interfered with by intermittent therapy than by continuous therapy. This observation may have no great significance in acute bacterial infections such as those caused by streptococci and pneumococci. It would have considerable practical value if the same general principle prevailed in the more chronic infections, such as tuberculosis, syphilis and staphylococcus infections. In other words, it is at least possible that the development of acquired immunity might be less suppressed by intermittent than by continuous therapy. It is an important question at the moment but there is very little evidence available concerning it.

DR. GINSBERG: One question comes to my mind along these lines. Since we are looking for a convenient and efficacious agent which will maintain continuous blood levels, perhaps it has been a mistake virtually to remove the sulfonamides from the armamentarium of the physician. It is practically not employed any more. Perhaps it is con-

sidered old fashioned. When properly used it is an effective agent, probably just as good as penicillin in pneumococcal and streptococcal pneumonia.

DR. McDERMOTT: It is an effective antimicrobial agent but I believe that its declining use is correct. The administration of aqueous penicillin is, after all, a fairly simple matter, as are also the more fluid preparations of penicillin in oil and beeswax. Another preparation, procaine penicillin, which is now under investigation, looks extremely promising, indeed much more promising than penicillin in oil and beeswax, provided it turns out to possess no significant toxicity. I think we are right in abandoning sulfadiazine because of its toxicity and relatively low antimicrobial potency. Do you agree with that, Dr. Horsfall?

DR. HORSFALL: I do not disagree. However, for the practitioner in the home the use of a form of penicillin requiring injection is a serious problem. This difficulty can be circumvented by increasing the dosage fivefold and giving the material by mouth.

DR. McDERMOTT: The use of sulfadiazine, as Dr. Ginsberg suggested, might partially solve the problem of Friedländer's pneumonia. All too often, cases of Friedländer's pneumonia admitted to the hospital go without a correct diagnosis during the first forty-eight hours, despite the fact that we have every facility with which to make it and there is sufficient awareness that such a condition exists. The organism is a diplobacillus which can look very much like a pneumococcus if one is examining a sputum smear at three o'clock in the morning. I believe that the difference between an excellent result and a chronic illness is probably determined in that first forty-eight hours. Would you agree to that?

DR. HORSFALL: Without any doubt.

DR. McDERMOTT: During that period too many of our patients receive penicillin therapy.

DR. WALTER MODELL: I think you have answered my question in part. I want to know how you treat patients with pneu-

monia prior to making the specific diagnosis. How would you treat patients with pneumonia if you had no facilities for making a specific diagnosis?

DR. McDERMOTT: If we had absolutely no facilities for making a specific diagnosis and there were no prospects of such within the next forty-eight hours, it would undoubtedly be safer to use sulfadiazine which at least might have some effect in Friedländer's pneumonia.

DR. MODELL: How long would you wait before you added another drug?

DR. McDERMOTT: If you had more than one drug and no diagnostic facilities, the thing to do would be to give both penicillin and sulfadiazine. You would then be covering all the bacterial pneumonias except tuberculous. This is, however, an extreme situation. Despite the fact that we often talk of practicing medicine in isolated areas with no diagnostic facilities, those areas are becoming rare. It is possible to obtain diagnostic facilities within a seventy-two-hour period in most places.

INTERNE: We have seen patients with pneumonia caused by an organism susceptible to penicillin but who do not seem to respond to penicillin therapy. On examination it does not appear that any complicating factors are present. How long would you be willing to continue with penicillin alone, before concluding that it was ineffectual and that you had better switch to another drug like sulfadiazine?

DR. McDERMOTT: It is a general problem in the management of pneumonia, namely, the patient who apparently has a bacterial pneumonia and who has received an antimicrobial agent but is not improving satisfactorily. Failure to respond may be usually suspected by the course during the second twenty-four-hour period. Certainly by the end of forty-eight hours, if the patient is just as ill as he was at the beginning, it is clearly apparent. Almost invariably that situation is not the result of the fact that an organism of a species usually sensitive to the drug is, for some peculiar reason, not sensitive to it in that patient. Generally, it is either not

pneumonia or one has made the wrong etiologic diagnosis of the pneumonia. For example, one may be treating Friedländer's pneumonia with penicillin. More commonly, in bacterial pneumonia some complication of the pneumonia is present, such as empyema or meningitis. Would you agree with that, Dr. Horsfall?

DR. HORSFALL: Yes, entirely.

DR. MUSCHENHEIM: In that connection, Dr. McDermott, it seems to me that the suppurative pneumonias are also ones which we always have to consider. These are of increasing importance since the prognosis in bacterial pneumonias has improved so much. An important problem in the differential diagnosis and management of pneumonia is that of making sure that there is no serious underlying primary disease like carcinoma, or that it is not a suppurative pneumonia or an early lung abscess.

DR. McDERMOTT: By "suppurative" pneumonia, do you mean a pneumonia breaking down into an abscess, either because of the nature of the pneumonia or as a result of some anatomic distortion?

DR. MUSCHENHEIM: It may be due to mixed infection.

DR. McDERMOTT: Would you tell us how you think you can distinguish them?

DR. MUSCHENHEIM: The response to treatment helps. The suppurative pneumonias may respond with defervescence and clinical improvement but the response may be only partial. It is not necessarily a complication of a primary pneumonia. It is a primary disease in which suppuration occurs, such as the suppurative pneumonias so commonly associated with carcinoma.

DR. McDERMOTT: We have been impressed with the fact that, in cases of empyema complicating primary pneumonia, penicillin makes the patient look and feel better. There is some improvement but conspicuous improvement does not occur until the empyema is discovered and drained. Is that the case in suppurative pneumonias?

DR. MUSCHENHEIM: Yes.

DR. McDERMOTT: Dr. Tompsett mentioned the antimicrobial therapy of streptococcal pneumonia and we talked about mild forms. Dr. Horsfall, have you any notion as to what we could accomplish with antimicrobial therapy today if we were faced with a pandemic of streptococcal pneumonia of the sort which was seen during World War I?

DR. HORSFALL: That is a very important question. I have heard it discussed by many people who had an opportunity to see hundreds of patients during World War I and it is their belief that present antimicrobial therapy might fail because of the time factor. A large proportion of patients who developed secondary bacterial pneumonia during the pandemic had such fulminating disease that there would have been no opportunity for the administration of adequate antimicrobial therapy. However, in those whose illness developed more slowly, I should think that the result might be exactly what one would expect now in primary bacterial pneumonias.

DR. McDERMOTT: That brings us to another point which is disturbing me a great deal. Many of the failures of current antimicrobial therapy in pneumococcal pneumonia are of that same type. The patient comes into the hospital late in a state of cardiovascular collapse which resembles a state of shock. He succumbs despite our best antimicrobial therapy, even though it is sufficient to inhibit bacterial growth to a point at which one is unable to obtain a positive culture. I am familiar with Dr. Stead's work which showed that the mechanism of that type of shock is different from the shock which occurs through blood loss or trauma and that there is no point in attempting to treat the shock of pneumonia as one would treat surgical shock. Have you any thoughts on that?

DR. HORSFALL: Yes, I have. We have treated or attempted to treat the peripheral vascular failure which so commonly precedes the fatal issue in pneumonia and have employed the measures generally used in

surgical shock. In all honesty, we accomplished nothing but to hasten the fatal issue. Certainly, we were never able to reverse it.

DR. McDERMOTT: You are referring to patients with a form of pneumonia which would be susceptible to antimicrobial treatment, provided you could reverse the shock. That is a very important point. We use antishock measures in these cases. The available studies, including Dr. Horsfall's own observations, however, indicate that they probably are of little or no value.

DR. GOLD: I wonder whether we could hear a little more about procaine penicillin from Dr. Tompsett. It is an interesting material.

DR. TOMPSETT: I will be glad to tell what little I know about it. Procaine penicillin is a crystalline salt formed from procaine hydrochloride and crystalline sodium penicillin G, which is relatively insoluble in water. There are several clinical investigations now in progress. The salt is put up in sesame oil or peanut oil which are, as you know, easily administered fluid preparations. It is thought that an insoluble salt of penicillin should be more slowly absorbed and hence provide more prolonged blood levels with a given amount of penicillin. This particular preparation, by all the means we have for evaluating it, looks exceptionally good thus far. As you know, a good preparation of penicillin in oil and beeswax will, after a single dose of 300,000 units, produce measurable blood levels for eighteen hours in approximately 75 to 90 per cent of patients and for twenty-four hours in about 50 or 60 per cent of patients. Thus far, with a similar dose of procaine penicillin, 100 per cent of patients had measurable blood levels for eighteen hours; 85 to 90 per cent for twenty-four hours; approximately 60 per cent or more at thirty and thirty-six hours and a significant number for as long as forty-two hours. In rare instances, measurable levels persisted for forty-eight hours. That for a single dose of 300,000 units looks good!

DR. McDERMOTT: What were the concentrations at thirty-six hours when penicillin was still measurable?

DR. TOMPSETT: The concentrations were remarkably high for penicillin administered with an absorption-delaying agent. Several were from 0.15 to 0.3 unit per cc.

DR. McDERMOTT: What do you think of the possibility of toxicity?

DR. TOMPSETT: There are possibilities of toxicity. The amount of procaine in 300,000 units of procaine penicillin is 120 mg. The toxicity of a single dose of 120 mg. is not great. That much, I believe, might even be given intravenously within a few minutes without very much danger. It would appear that the only real likelihood of difficulty would arise in those patients who are hypersensitive to procaine. This would not seem to constitute a very serious problem but it should be kept in mind. I wonder what Dr. Gold thinks about the toxicity of procaine?

DR. GOLD: I should think that such doses would be quite safe. There are, of course, individual patients with unusual susceptibility to procaine and every once in a while one hears of a disaster from a small dose which got into the circulation too quickly.

DR. McDERMOTT: Is this cocaine or procaine?

DR. GOLD: It is true of cocaine but I was speaking of procaine. The safety of procaine as used by the anesthetists lies chiefly in the fact that it is given subcutaneously. They seldom give procaine intramuscularly. In the case of procaine penicillin, of course, one is injecting into the muscle and that results in a situation of a different order from the standpoint of toxicity.

DR. McDERMOTT: What do you think of the experience with the use of procaine in the treatment of peripheral vascular diseases? It has been given intravenously in doses of 4 mg. per Kg. two or three times a week.

DR. GOLD: It is fairly safe there and I think it is fairly safe in the case of the penicillin preparation. There are those isolated cases of hypersensitivity but I doubt very

much that they ought to influence the use of material like this if it turns out to be an important form of therapy. There is another point I should like to raise. Would not this procaine penicillin do away with the intermittent aspect of treatment? I gained the impression that periods of subeffective concentrations of penicillin in a regimen of treatment may have some advantage.

DR. McDERMOTT: It might have advantages in some situations but I do not think intermittent therapy has any advantage in the acute infections such as bacterial pneumonia.

DR. GINSBERG: There is another possible complication in the use of procaine penicillin. Do you have any idea how long it takes before the procaine is excreted?

DR. TOMPSETT: No, as yet I do not have that information.

DR. GINSBERG: The point I am trying to make is that procaine is a sulfonamide-inhibitor. In the event that one should give it to a patient to whom one would later need to give sulfonamides, the latter drugs would have no effect until the procaine had disappeared or until it had reached a very low concentration.

DR. McDERMOTT: The procaine penicillin is absorbed over a period of four or five days. If it is given daily for a long period, that could be a real problem.

DR. GINSBERG: It has been shown in patients given large doses of procaine for local anesthesia that they may absorb enough procaine to cause their blood to develop antisulfonamide activity.

DR. MODELL: How much sulfonamide does 1 mg. of procaine inactivate?

DR. HORSFALL: One mg. of procaine will inactivate about 1 Gm. of sulphonamide.

DR. CATTELL: If the combination is absorbed very slowly, wouldn't the procaine absorption be spread out over a long period of time, just like that of penicillin? Unless the combination has a special toxic property, we can assume that the procaine will be destroyed very quickly. In an animal you can give half a fatal dose every twenty minutes with safety.

DR. McDERMOTT: That was Dr. Tompsett's point. Even if the total amount used over a period of ten days went into the circulation at one time, it would be less than a fatal dose. I think Dr. Gold's point is very well taken, however, that if a drug can produce a reaction, one must think of the possibility of that reaction in connection with its administration.

VISITOR: Would you comment on the use of penicillin aerosol?

DR. McDERMOTT: It has limited usefulness. It is an effective way of treating pneumococcal pneumonia but other methods are more convenient. The aerosol maintains effective concentrations of penicillin in the blood but on the whole I believe that for practical purposes the other methods are superior.

INTERNE: I am wondering about the syndrome called "unresolved pneumonia," or the persistence of an x-ray shadow after the patient apparently feels well in every way. Do you believe there is such a thing as unresolved pneumonia?

DR. McDERMOTT: I suspect there is. It is infrequent but I suspect we will see more of it. The usual case called "unresolved pneumonia" probably never was pneumonia, as you are obviously hinting. It was tuberculosis, or perhaps a carcinoma of the lung. I do believe there is a small group of very elderly patients who would have died of pneumococcus pneumonia prior to the days of antimicrobial therapy and who are being saved or whose illness is being converted into a chronic illness by the new therapy. In some of these patients resolution is incomplete and healing occurs by fibrosis. Have you any ideas on that, Dr. Horsfall?

DR. HORSFALL: I think it will be seen occasionally in younger persons. Already we have seen it in two persons under thirty.

DR. McDERMOTT: Were they patients who had been extremely ill?

DR. HORSFALL: Very ill indeed and with extensive pneumonia. There was no question about the diagnosis and even subsequent examinations by bronchoscopy

revealed no adequate explanation for the unresolved pneumonia.

DR. McDERMOTT: Is it your belief that these patients might not have survived prior to the advent of effective antimicrobial therapy?

DR. HORSFALL: Yes. I am inclined to agree with you that it only occurs in the extremely ill.

DR. GOLD: What proportion of the patients with pneumonia who come into the hospital now have primary atypical pneumonia?

DR. McDERMOTT: In our own service, which is small, it varies. During the winter we may see a great deal of pneumococcal pneumonia and no atypical pneumonia. Then we may have an outbreak of atypical pneumonia. In our service this usually occurs in the late summer and fall. I believe Dr. Horsfall would know whether atypical pneumonia tends to occur in outbreaks, or whether there is a steady month-by-month incidence of it now.

DR. HORSFALL: I think all the evidence suggests that the incidence is relatively constant, far more so than that of bacterial pneumonia. The incidence is somewhat lower in the summer than in the winter.

DR. McDERMOTT: Is it the most common form of pneumonia?

DR. HORSFALL: At one military installation, where all patients with a fever of 101°F. or more are screened because they must go through the station hospital, there were more than 250 patients in the last year with pneumonia among a total population of about 6,000. Only six of these patients had bacterial pneumonia.

DR. GOLD: The term "virus pneumonia" has not been mentioned in this conference. Practitioners use it freely. How does it apply?

DR. TOMPSETT: The term "primary atypical pneumonia" is used to describe a clinical syndrome which is probably caused by a number of different etiologic agents. Because it is suspected that most of these agents are viruses, the term "virus pneumonia" has come into common usage. It

seems preferable, however, to avoid using the term "virus pneumonia" at least until the virus etiology has been established and then a more specific term should be available, as has been the case in psittacosis.

SUMMARY

DR. TOMPSETT: The conference this afternoon has helped to crystallize some of the problems in the treatment of primary pneumonia which have arisen in connection with the development of the highly effective antimicrobial therapy, namely, penicillin, sulfadiazine and streptomycin. After one has made a diagnosis of primary pneumonia, how important is it in these days to establish the causative agent? Is it safe to ignore the causative organism and proceed directly to treat with penicillin? It appears to be the consensus of opinion that detection of the causative organism is still a matter of great importance. If all bacterial pneumonias were due to the pneumococcus, the matter would be very simple because of the ease with which they can be controlled with an antimicrobial agent virtually without toxicity, namely, penicillin, but these constitute only about 95 per cent of the bacterial pneumonias. Most of the others include those due to streptococci, staphylococci, tubercle bacilli and Friedländer's bacilli. Clinically, these cases are often difficult to differentiate, yet it is imperative to do so because their treatment differs. Whereas pneumococcus pneumonia shows dramatic response within twenty-four to forty-eight hours after moderate doses of penicillin, the streptococcus and staphylococcus pneumonias require much larger doses. Special emphasis was laid on the problem of Friedländer's pneumonia. This organism does not respond to penicillin and is best treated by a combination of sulfadiazine and streptomycin. In this disease irreversible changes may be produced within forty-eight hours, so that a delay in appropriate therapy by a mistaken diagnosis may prove disastrous. The satisfactory response to streptomycin of patients with acute tuberculous pneumonia in the exuda-

tive stage adds further weight to the importance of early recognition of the causative agent.

A noteworthy feature of the discussion was the emphasis placed on the so-called primary atypical pneumonias, sometimes referred to as "virus" pneumonias, due to as yet unidentified organisms some of which may be viruses. While the incidence of primary atypical pneumonias is not established, it is clear that they occur very frequently and indications are that their milder forms far exceed those of bacterial pneumonias. These do not respond to any known antimicrobial agents and in them therapy consists essentially of supportive measures applied in relation to symptoms that arise.

The discussion also embraced such items as the need for typing the pneumococcus, the place of the sulfa drugs in the treatment of pneumonias, the causes of failure to respond to therapy, and the various plans

for the use of the antimicrobial agents. It was pointed out that when sulfadiazine is necessary, 2 Gm. may serve as the initial dose followed by 1 Gm. every four hours. In the case of streptomycin, the usual dose is from 20 to 40 mg. per Kg. daily or about 1 to 2 Gm. a day for the average adult by intramuscular injection in three or four fractions. Interesting experience was related showing that current schedules of intramuscular injection of penicillin at intervals of three to four hours in the treatment of pneumococcal pneumonia may no longer be necessary and equally satisfactory results may be obtained by the intramuscular injection of 300,000 units dissolved in 1 cc. of saline and given at intervals of twelve to twenty-four hours. The discussion also touched on a new procaine-penicillin compound which, by virtue of the fact that it is insoluble, may produce unusually sustained high blood levels after a single dose. This is still in the experimental stage.

Clinico-pathologic Conference

Pulmonary Disease of Unknown Origin*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient F. B., (B. H. History No. 138724), a forty-five year old white married housewife, entered the Barnes Hospital for the first time on August 22, 1946, complaining of cough of approximately two years' duration. The family history was non-contributory. The past history was of interest in that the patient had had typhoid fever as a child. She stated that she had never enjoyed good health nor had she been robust and her appetite had been poor for a number of years. Prior to marriage she worked in a newspaper office and had been extremely fatigued at night. However, she had been free of symptoms of any definite illness until 1942, at which time she developed complaints referable to the gastrointestinal tract. X-ray studies were said to have revealed a pathologic gallbladder and at the same time she was told that she had a "positive test for brucellosis"; the nature of the diagnostic procedure was not known. At that time "vaccine therapy" was begun and it was continued for four years, being discontinued only two months prior to her admission to this hospital. At no time had she had symptoms which suggested brucellosis. In March of 1945, because of irregular and prolonged menstrual periods, the patient underwent dilatation and curettage of the uterus. Extreme hyperplasia of the endometrium was said to have been found and total hysterectomy was subsequently performed. Subsequently she was given monthly injections of "20,000 units of an estrogenic substance." Postoperatively, she

developed an upper respiratory infection and cough and lost about 15 pounds in the ensuing six months. In January, 1946, flatulence again appeared and gastrointestinal roentgenograms were made. They were said to have shown "a dilated 2nd and 3rd portion of the duodenum"; concomitantly, the patient noted stiffness, swelling and some redness about the phalangeal joints which persisted for a few months and then subsided spontaneously. She was seen in a diagnostic clinic in Chicago where a number of studies were performed and among them a normal chest film was recorded. Her abdominal complaints, particularly fullness and tightness of the upper abdomen immediately after eating, persisted and she had occasional nausea and vomiting for ten to thirty minutes after meals which relieved her symptoms. She restricted her diet to 1 quart of milk a day, lettuce, carrots and graham crackers. Her weight fell to 90 pounds. Further x-ray studies were made and the patient was told that she had "a sinus infection" but that her chest films continued to be negative. On examination her abdomen was described as showing a "doughy resistance" but no other abnormalities were detected.

Laboratory studies, according to reports received from the clinic in Chicago, indicated that the patient's red blood count was normal. Her urine contained a trace of albumin and the blood non-protein nitrogen, cholesterol, calcium and phosphorus were all said to have been within

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

normal limits. The basal metabolism rate was -8 . She was admitted to a hospital where a laparotomy was performed to "elucidate the roentgenographic findings." The operative note stated that the only abnormalities consisted of a small, shrunken, knobby spleen and dilatation of the 2nd and 3rd portions of the duodenum. The gallbladder was said to have appeared normal and the site of the previous operation was well healed. No adhesions were present. The kidneys were normal to palpation. A mesenteric lymph node was removed and on subsequent microscopic study was reported as showing only chronic inflammation. Duodenojejunostomy was performed. At the time of her discharge from the outside hospital the patient weighed only 84 pounds.

As stated, the patient had had an upper respiratory infection with cough following her hysterectomy two and one-half years previously. Subsequently, cough had occurred in association with a postnasal discharge in the morning. Shortly after her second abdominal operation and one month prior to her admission to the Barnes Hospital, the patient again began to note a persistent cough which was described as severe, was present both day and night and was productive of purulent sputum; at no time was the sputum bloody. The patient also stated that she had had some dyspnea on exertion and slight swelling of the feet and ankles at night. Although she occasionally had pain in the left chest, at no time did she note chills or night sweats and her maximum temperature had been 100°F .

Physical examination on entry revealed the patient's temperature to be 38.5°C ., pulse 120, respirations 44 and blood pressure 120/60. She was an emaciated, rather dehydrated female who looked much older than her stated age. She coughed frequently and complained of pain throughout the left chest and upper abdomen. Chest excursion appeared limited because of pain. The skin was warm and no eruption was seen. Examination of the eyes revealed that the pupils reacted well and the optic

fundi were normal. The left ear drum was dull and somewhat retracted. Mucopurulent secretions were present in the nares and the pharynx appeared granular; lymphoid hyperplasia was seen. A mucopurulent discharge likewise covered the posterior pharynx. The tonsils were slightly enlarged. There was kyphoscoliosis of the spine and chest was therefore asymmetric. Retraction of the left ninth, tenth and eleventh interspaces on inspiration was described and over the left chest posteriorly resonance was impaired and tactile fremitus, breath sounds and voice sounds were diminished. A few moist râles were heard throughout both lungs. Except for the rapid rate the heart appeared normal to examination. Two abdominal scars appeared well healed. On examination of the abdomen there was tenderness in the right upper quadrant but no organs or masses were felt. The fingers were not clubbed and there was no edema. The remainder of the physical examination was negative.

The laboratory studies were as follows: Blood count: red cells, 3,830,000; hemoglobin, 10.2 Gm.; white cells, 22,200; differential count: stab forms, 13 per cent; segmented forms, 68 per cent; lymphocytes, 16 per cent; monocytes, 3 per cent. Urinalysis: albumin, trace; sediment, many white blood cells. Stool: guaiac negative. Blood Kahn test: negative. Sputum examination: no acid-fast bacilli seen. Blood chemistry: fasting sugar, 63 mg. per cent; non-protein nitrogen, 13 mg. per cent; total protein, 5.8 Gm. per cent; albumin, 3.0 Gm. per cent; globulin, 2.8 Gm. per cent. Electrocardiogram: normal. Roentgenogram of the chest (Fig. 1): "The cardiac silhouette and the aorta are within normal limits. There is a dense infiltration in the perihilar region on the left side extending out to the lateral zone of the lung; its margins are very well demarcated and it appears lobulated. In the oblique view the abnormal findings are located in the left lower lobe. There is generalized haziness over the entire lower left chest, suggesting the presence of a small amount of fluid.



FIG. 1. Roentgenogram of the chest taken during the first admission. There is bilateral pulmonary infiltration and fluid is present in the left pleural cavity.

On the right side there is a dense infiltration in the inferior portion of the hilus but the margins are not well demarcated; lung markings are slightly coarse along the descending bronchi in this area. The exact nature of these masses is not known but it is thought that they represent a tumor in both perihilar regions with fluid in the left pleural cavity."

During her stay in the hospital the patient coughed almost incessantly and continued to produce mucopurulent sputum which on repeated examinations contained no acid-fast bacilli. On culture, coliform organisms were reported. The patient was transferred to the Chest Surgical Service and a thoracentesis was done. Three-hundred cc. of amber bloody fluid were obtained which clotted promptly. On culture, no organisms were noted and cultures for fungi on Sabouraud's medium were likewise negative. Some of the material was inoculated into a guinea pig but the animal remained

well. Cell blocks were made on the sediment and no tumor cells were seen in the sections of these.

A bronchoscopy was performed and no abnormalities were found other than inflammation of the bronchial mucosa. The mucosa was biopsied and was reported as showing only chronic inflammation. The patient's temperature ranged between 38 and 39°C. and did not respond favorably to penicillin therapy. Agglutination tests for brucellosis were reported positive in a dilution of 1:320. Because no definitive diagnosis could be made, the patient was exposed to treatment with roentgen rays. About three weeks later she began to improve; the cough lessened, the fever subsided and the chest signs cleared although signs of consolidation or fluid at the left base persisted and some râles were still audible. Subsequently, there appeared to be an increase in fluid in the left pleural cavity but no other changes in the pulmonary findings. The patient was transferred back to the Medical Service and on examination at that time her liver was palpable 8 cm. below the right costal margin and there was bilateral ankle edema. The patient complained of moderate diarrhea. She was given a high protein diet, large amounts of vitamins and two blood transfusions. Further laboratory studies were as follows: Blood count: red cells, 4,250,000; white cells, 13,350. Total protein: 5.1 Gm. per cent; albumin, 2.4 Gm. per cent; globulin, 2.7 Gm. per cent. Icterus index: 6; cephalin-cholesterol flocculation, 3+. Examinations of the sputum and of the gastric washings were continued but at no time were tubercle bacilli found. Just prior to discharge the patient was again examined on the Chest Service and clearing of the infiltrative lesions was described; the fluid in the left pleural cavity persisted. The liver had decreased in size and the edema had diminished. When the patient left the hospital on September 6, 1946, she appeared to be in better health and stated that she felt much improved. She returned to her home and the care of her private

physician. During the first two months she remained at home her appetite improved and she gained weight. The cough bothered her much less and she seemed to be getting on quite well until three weeks before her second and last admission at which time the cough again increased and hoarseness appeared. Her temperature, which had been normal, rose to 101°F. and anorexia and great fatigue were again noted; on December 14, 1946, the patient was readmitted to the Barnes Hospital.

All the time of entry her temperature was 38°C., pulse 110, respirations 30 and blood pressure 110/70. She appeared extremely emaciated and very ill. She was orthopneic and dyspneic and could speak only in a harsh whisper. Respirations were punctuated by frequent paroxysms of cough productive of thick yellowish-green sputum. The nares contained purulent secretions. Expansion of the left chest was limited and there was dullness over the lower half of both lungs posteriorly. Over the areas of dullness breath sounds and voice sounds were diminished and the breath sounds were bronchovesicular in character. Moist râles were heard bilaterally above the areas of dullness. The heart seemed normal to examination. The liver edge was questionably felt 5 cm. below the costal margin and clubbing of the fingers had appeared. Laboratory data included the following: Blood count: red cells, 4,680,000; hemoglobin, 14.4 Gm.; white cells, 15,000; differential count: eosinophiles, 1 per cent; stab forms, 11 per cent; segmented forms, 69 per cent; lymphocytes, 12 per cent; monocytes, 7 per cent. Urinalysis: negative. Venous pressure: 150 mm. of water. Circulation time (decholin): 15 seconds. Vital capacity: 450 cc. Sputum examination: negative for acid-fast organisms. Blood chemistry: non-protein nitrogen, 21 mg. per cent; total protein, 5.8 Gm. per cent; albumin, 2.6 Gm. per cent; globulin, 3.2 Gm. per cent. Roentgenogram of the chest (Fig. 2): "There is no evidence of fluid in the left pleural cavity. Fibrosis extends outward from both hilar regions and is



FIG. 2. Another roentgenogram of the chest made during the second admission. There has been an increase in the amount of fibrosis but the pleural effusion is no longer present.

greater in extent than was previously noted but its density does not appear increased."

The patient was seen in consultation by an otolaryngologist. On laryngoscopic examination of the larynx he found the mucous membrane to be dull red in color; there was thick yellow pus on the posterior wall of the hypopharynx. The arytenoids moved normally. There was crusting involving the anterior third of the larynx and considerable crusting below the cords but no evidence of tumor was noted. It was thought that the hoarseness was a result of the pulmonary infection with drying of the secretions around the larynx. The patient remained critically ill; her temperature ranged between 38 and 39°C. and her pulse averaged 130. Weakness was extreme and symptomatic treatment brought no improvement. Two days after admission she was found sitting upright in bed, confused and unresponsive. The signs in the lungs

had not changed from those recorded on admission. Cyanosis was present and pitting edema of the ankles had reappeared. The white blood cell count had risen to 26,500. In spite of the administration of oxygen and penicillin the patient failed to improve and she died on December 27, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient was in the Barnes Hospital on two occasions and each time was exposed to all the diagnostic facilities available; yet on neither occasion could a diagnosis be established and the problem still remains for us today to attempt to establish the nature of the pulmonary lesion. Likewise, the question of whether the patient had other visceral lesions must be considered, particularly in view of the fact that at the time of her second laparotomy the spleen was described as small and knobby. It seems probable that the patient had hepatic involvement and it is conceivable that all of her lesions were related. In reviewing the history it is interesting to note that approximately two years before her final illness she developed some respiratory symptoms, particularly cough, following a hysterectomy. We are told, however, that at the time of onset of the symptoms she was seen in a clinic in Chicago and had a negative chest film; furthermore, a negative chest film was reported as recently as one and one-half months prior to entry here. If that information is correct, we are probably dealing with a fairly acute process and we must prove that the lesions which were found in a chest film taken on admission to this hospital had not been present some months before. Dr. Goldman, the radiologists interpreted the first chest film as indicating the presence of a tumor; in view of the course and the other information available do you agree with that diagnosis?

DR. ALFRED GOLDMAN: I think that at that time I would have made the same suggestion. The hilar lesions were bilateral and certainly suggested malignancy.

DR. ALEXANDER: Do you believe that the patient could have developed a lymphoma or metastases from a bronchogenic carcinoma in one month?

DR. GOLDMAN: No, I think that period of time is probably much too short.

DR. ALEXANDER: What is your opinion, Dr. Moore, in regard to the development of a mediastinal lymphoma in a period of one month?

DR. CARL V. MOORE: I do not believe this patient had a lymphoma but lymphomatous enlargement of the mediastinum may appear very rapidly, even within one month. My reasons for discarding that diagnosis in this particular instance lay in the absence of other signs. If the patient had had Hodgkin's disease or lymphosarcoma, one would have expected that at some time during the course of her illness she would have developed enlargement of some other lymph nodes. There was neither lymphopenia nor monocytosis and although the absence of these does not rule out Hodgkin's disease, it makes it quite unlikely. Further, splenomegaly and severe anemia would be expected had this been a lymphomatous disease. I believe all of the considerations enumerated mitigate strongly against that possibility.

DR. ALEXANDER: If the patient had a lymphoma, could the apparent respiratory infection be related to it?

DR. C. V. MOORE: No, I believe the infection would have to be considered as a separate, unrelated entity.

DR. ALEXANDER: From the data at hand, we are led to believe that the infection involved the sinuses, the larynx and the bronchi. Dr. Harford, have you any suggestions as to the etiology of this rather widespread process?

DR. CARL G. HARFORD: I was impressed by the fact that the patient's cough originally appeared shortly after an abdominal operation and also by the fact that on both examinations here purulent secretions were described in the upper respiratory tract. It seems conceivable to me that during the course of the operation exudate in the upper

respiratory tract was aspirated into the lungs and gave rise to one or more lung abscesses.

DR. ALEXANDER: Your point is very well taken. Aspiration pneumonia must certainly be considered. In view of the fact that coliform bacilli were cultured in the sputum, I should like to ask whether colon bacilli are commonly found in gastric secretions.

DR. HARFORD: They may occur there occasionally.

DR. ALEXANDER: Dr. Wood, do you think that there is any direct connection between the abdominal operation and the finding of colon bacilli in the sputum?

DR. W. BARRY WOOD, JR.: No, I do not think so. I am impressed, as Dr. Goldman is, by the response of the pulmonary lesion to x-ray therapy. It seems to me that this observation rules out most of the common infections.

DR. ALEXANDER: Tuberculosis must be considered but attempts to substantiate that diagnosis by the finding of tubercle bacilli in the sputum were pursued diligently and no acid-fast bacilli were ever found. If this had been tuberculous pneumonia, Dr. Goldman, do you think that tubercle bacilli would have been found?

DR. GOLDMAN: I would certainly think so.

DR. ALEXANDER: When Dr. Thomas Burford bronchoscoped the patient, he noted the inflammatory changes described in the protocol. X-ray therapy was given in the hope that liquefaction of the area of induration in the lung might be achieved, thus making it possible for the patient to cough up the necrotic material more easily.

DR. DONALD S. BOTTOM: The patient received more exposure to radiant energy than one would advise for the treatment of an infection. The total dosage given was designed to effect a radiosensitive tumor, a therapeutic trial as it were.

DR. ALEXANDER: I should state that there was some controversy in the Chest Service as to the diagnosis. Some members believed that the patient had a tumor, perhaps one of the lymphomas. Boeck's sarcoid was also mentioned.

DR. BOTTOM: The clinical diagnosis which we received was, "questionable tumor of both lungs of unknown origin," and it was on the basis of this diagnosis that the patient received the amount of radiation given.

DR. ALEXANDER: Would the amount of x-ray administered have aided in breaking down an indurated lung?

DR. BOTTOM: It probably would have led to more destruction than would have been desirable. The amount of radiant energy given would have reduced a very sensitive tumor in size; but had the patient had inflammatory induration of the lung, abscess formation probably would have occurred.

DR. ALEXANDER: It might be well for me to summarize the opinion of the members of the Chest Surgical Service. The record stated, "It was felt by some that the most likely diagnosis was a malignant lymphoma of the mediastinum. Dr. Evarts Graham felt that a bilateral inflammatory process was more likely." Here, aspiration pneumonia has been suggested and no conclusive support for malignancy has been forthcoming.

DR. BERTRAND Y. GLASSBERG: I believe this patient may have had a systemic infection which was quiescent until a few months before her death. One remote possibility worthy of mention is histoplasmosis. I am unaware of the sensitivity of pulmonary histoplasmosis to radiant energy.

DR. BOTTOM: As far as I know, pulmonary infection due to *Histoplasma capsulatum* is not favorably influenced by x-ray therapy.

DR. ALEXANDER: Was not the white blood cell count rather high for histoplasmosis?

DR. WOOD: Yes. In typical cases white cell counts of a much lower order are seen.

DR. ALEXANDER: Although the patient received "vaccine treatment" for brucellosis, at no time could she have symptoms suggestive of that disease and it seems to me unlikely that the pulmonary findings could be explained on that basis.

DR. MARGARET L. J. HENRY: Is it possible that the repeated injections of brucella vaccine produced a state of hypersensitivity and a generalized vascular disease?

DR. ALEXANDER: That is a very interesting suggestion since we know that the patient did receive vaccine therapy for years; however, since the exact nature of the vaccine is not known we cannot comment on its antigenicity. I think the possibility of fungus infection in the lung must be mentioned in passing although repeated specimens of sputum were cultured on Sabouraud's medium and no organisms were recovered.

DR. GOLDMAN: One must consider actinomyces, blastomycosis or torulosis but in most of these skin lesions are seen and the negative results on bacteriologic study tend to rule them out.

DR. ALEXANDER: Dr. Wade, would you comment on the possibility of liver disease?

DR. LEO J. WADE: The laboratory data suggest liver involvement as evidenced by a 3+ cephalin-cholesterol flocculation test and the reversal of the albumin-globulin ratio. Of course, if the pulmonary infection were due to a chronic granuloma, one might well find elevation of the serum globulin. However, if there were no chronic granuloma in the lung, the reversed albumin-globulin ratio would point to primary liver disease. Furthermore, the anemia is consistent with hepatic involvement. I do not believe, however, that the patient had cirrhosis.

DR. ALEXANDER: What type of granulomatous lesion did you have in mind?

DR. WADE: I was referring to the chronic infections already mentioned.

DR. GOLDMAN: Two other diagnostic possibilities should be mentioned in passing. First, there is no history of repeated use of oil-base nose drops but lipoid pneumonia is one of the causes of chronic pulmonary inflammation such as may be present here. It seems entirely conceivable that this patient, who had a chronic upper respiratory infection, may have used some such oily preparation. Likewise, pulmonary ade-

nomatosis may give a radiologic picture such as seen here and, although rare, may be considered.

DR. ALEXANDER: Are the lesions of pulmonary adenomatosis radiosensitive?

DR. BOTTOM: There have been so very few cases reported that I am unable to answer your question.

DR. ALEXANDER: I think both of Dr. Goldman's suggestions are excellent; either one of them could have given rise to the course observed in this case.

DR. WOOD: Dr. Alexander, have you completely discarded Boeck's sarcoid as a diagnostic possibility?

DR. ALEXANDER: Yes, I have. Do you think it merits further consideration, Dr. Wood?

DR. WOOD: Yes, I do, for I do not see how it can be ruled out on the basis of the data available.

DR. GOLDMAN: The response to x-ray which this patient exhibited is compatible with sarcoid and the bilateral hilar enlargement likewise is consistent.

DR. ALEXANDER: The course seems too rapid for sarcoid in my experience.

DR. WADE: Although the patient eventually developed a reversal of the albumin-globulin ratio, at no time was the serum globulin elevated *per se*.

DR. ALEXANDER: I am not sure that hyperglobulinemia is a universal finding in sarcoid although it is certainly very common.

DR. WADE: I agree Dr. Alexander with your statement, but I would expect the globulin value to be at the upper limit of normal in any case.

DR. ALEXANDER: In summary, then, one may say that a number of diagnoses have been suggested to explain this very complex clinical picture; included have been malignant lymphoma, chronic infections such as tuberculosis and fungus disease, sarcoid, lipoid pneumonia and pulmonary adenomatosis. I am afraid we will have to rely on the pathologists to clarify the situation, however, for we have been unable to rule in or out definitely any of the possibilities.

Clinical Diagnoses: ?Malignant lymphoma of the mediastinum; ?chronic pulmonary infection; ?sarcoid, lipoid pneumonia or pulmonary adenomatosis.

PATHOLOGIC DISCUSSION

DR. BETTY B. GEREN: At autopsy the body was that of a well developed but very poorly nourished white woman who weighed 42 Kg. There were circular areas of depigmentation about the mammary areoli. The heart weighed 270 Gm. and there was slight sclerosis of the coronary arteries. The liver weighed 1,550 Gm. and was soft in consistency; there were yellowish white markings in the periphery of the lobules as seen on section. The gastrointestinal tract was essentially normal except for small erosions of the gastric mucosa. The kidneys were slightly granular and weighed 190 Gm. each. The spleen was very small, weighing only 35 Gm.; there were two whitish pyramidal foci at its periphery measuring 0.5 cm. in diameter. The uterus, ovaries and fallopian tubes were absent.

The lungs weighed 1,130 Gm.; over the pleural surfaces there were a large number of clear and fibrous adhesions. The right pleural space contained 100 cc. of sero-sanguineous fluid and the left pleural space contained about 500 cc. of similar fluid. The tracheobronchial tree contained a moderately large amount of thick, yellowish, purulent material. On section of the lungs there were three types of nodular lesions. Scattered through all the lobes of both lungs were firm, yellowish, granular, slightly elevated nodules varying from 0.5 to 1.5 cm. in diameter, some of which showed small, white, firm foci at their centers. The second type of nodule was extremely firm, pale yellow-white in color, sharply circumscribed and slightly bulging; these varied from 1 to 2 cm. in diameter and were found in the lower lobes of both lungs. In the left lower lobe these nodules formed a large mass which involved the pleura and the adjacent soft tissues of the chest wall and measured 8 by 5 by 2 cm. The third type of nodule was found in the lobes of the left lung; in the

upper lobe there was a 2.5 by 1 by 1 cm. irregularly shaped focus that was firm and bright yellow. The pulmonary parenchyma around the focus showed atelectasis with an increased amount of edematous interstitial fibrous tissue. In the left lower lobe there was a 1 by 1 by 1 cm. bright yellow, moderately firm lesion which was flat when cut; it was surrounded by pulmonary tissue which likewise was partially replaced by edematous fibrous tissue. On the posterior surface of the right lower lobe there was a 4 by 4 by 0.3 cm. opaque, slightly retracted focus of pleural thickening. The pulmonary parenchyma underlying this focus showed changes similar to those seen throughout the right lower lobe, that is, considerable increase in fibrous tissue.

DR. ROBERT A. MOORE: I think that this case will be particularly enlightening if I present it to you much as it was unfolded to us as we studied it. You will remember that on the basis of the gross examination the two organs that showed major pathologic changes were the lungs and the spleen. The spleen was small and firm and from the gross examination one could make no other diagnosis than "atrophy of the spleen." In the lung there was a disease process producing irregular nodules of varying size, yellow and grey in color, associated with fibrosis in some areas and with only a small amount of fibrous proliferation in other areas. Thus, our gross diagnosis at the time of autopsy was that of a chronic granulomatous disease involving the lungs and possibly the spleen. Figure 3 is a section of the lung, showing a bronchus. There is metaplasia of the epithelium and destruction of the wall. The lumen extends almost to the muscle which indicates that most of the tissue in between has been destroyed. In the lumen there is an exudate consisting of fibrin and polymorphonuclear leukocytes and in some places the exudate is undergoing necrosis. Larger cells are seen, macrophages, which are filled with numerous vacuoles which probably contain fat. In Figure 4, in another area of the lung, the typical picture of acute bronchopneumonia

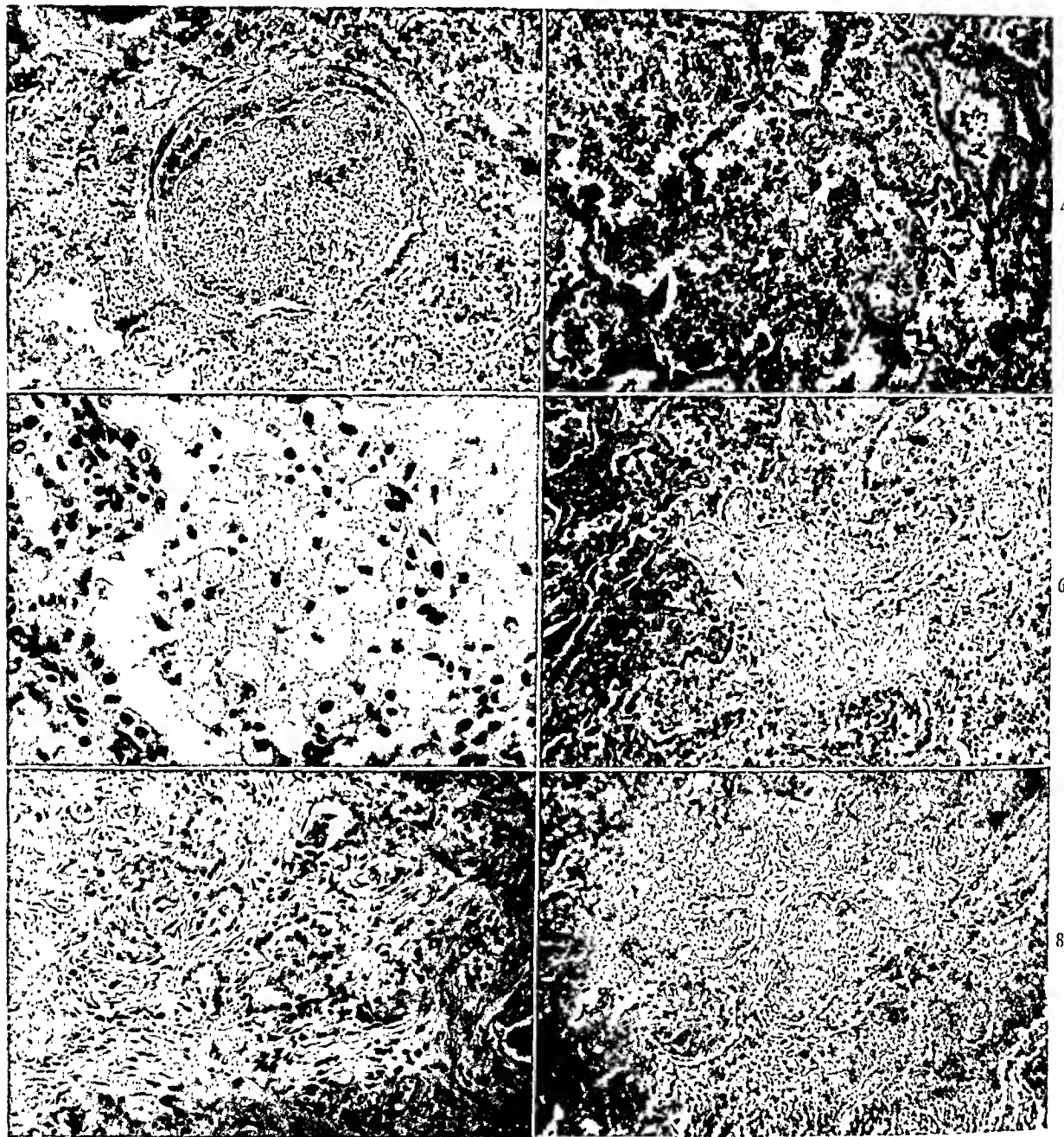


FIG. 3. Section of the lung showing a small bronchus. Note destruction of the wall. The exudate contains macrophages which are filled with vacuoles, probably fat.

FIG. 4. Another section of the lung showing an area of acute bronchopneumonia. Here the exudate contains chiefly polymorphonuclear leukocytes.

FIG. 5. Higher power view of the lung showing the macrophages distended with fat globules.

FIG. 6. Section through an area of organizing pneumonia.

FIG. 7. Another area of the lung which has undergone fibrotic changes. Note that the tissue spaces are lined with cuboidal epithelium.

FIG. 8. Still another section through the lung showing an area where necrosis has occurred.

may be seen. The alveolar walls are not thickened and the alveolar spaces contain only a small amount of fibrin. Numerous polymorphonuclear leukocytes are present. In another section of the lung (Fig. 5), the alveoli are filled with large macrophages which are tremendously distended with fat globules; special fat stains showed that each of the small vacuoles seen in the macrophages represented a tiny droplet of fat and, indeed, this finding constituted one of the most prominent features of the microscopic examination of the lung. It should be noted that cuboidal cells line the surface of the alveolar wall, an indication of chronic disease in the lung. In Figure 6 another region of the lung is shown and the pathologic picture is typical of that seen in organizing pneumonia. The alveolar spaces have been replaced in part by fibrillary tissue and some of the fat-laden macrophages are isolated within the fibrous tissue. In the periphery of this section the process represents the changes of an acute pneumonia such as was seen in Figure 2. Figure 7 shows an area of fibrosis in the lung. In the gross examination it appeared as grey, dense, moderately mature connective tissue. Here the spaces are lined with cuboidal epithelium. In Figure 8, a mass of pulmonary tissue undergoing necrosis is seen. The nuclei have disappeared in the necrotic area and the boundary between the living and necrotic tissue is relatively sharp.

Sections of the spleen showed extreme atrophy and fibrosis. The Malpighian bodies were practically absent and in a few areas foci of necrosis were seen. The liver showed a small amount of fatty infiltration and central necrosis of recent origin but no other lesion which could be related to the major process. Microscopic examination of the other organs revealed no significant abnormalities.

Our problem, of course, was to attempt to determine the nature of the disease which led to this patient's death. One of the first considerations is to remember the organs involved. They include the lungs, liver and spleen. The atrophy of the spleen does not

seem to me to be specific and for that reason I am of the opinion that the changes have no bearing on the principal disease from which the patient suffered. The changes in the liver were likewise not of sufficient magnitude to be considered part of the major disease. The central necrosis probably resulted from anoxia during the terminal stage of the patient's life. The lymph nodes contained no specific lesions related to those found in the lungs and can be discarded as having no bearing on the major disease. We thus come to the point where it appears that the major disease process in this patient involved only the lungs.

Let us summarize again the character of the pulmonary disease. First, there was exudative inflammation of the acute variety with polymorphonuclear leukocytes and fibrin. Second, bland foci of necrosis up to 7 mm. in diameter were seen. Third, a prominent part of the picture was the presence of many macrophages containing a large number of finely divided fat particles. Fourth, there was an organizing pneumonia and fifth and finally, areas of fibrosis were common. I believe it is helpful to list these five features, for in arriving at the etiology of the changes it is necessary to find an agent that is capable of producing changes covering the entire range of inflammation, that is, from acute inflammation to fibrosis. Of the diagnostic suggestions made in the clinical discussion, certainly neoplasm may be ruled out immediately for there is no evidence of any malignant process. As to infectious agents which may have produced this disease it was pointed out that conceivably the tubercle bacillus could have been responsible. Brucellosis can likewise produce lesions of the type seen here but does not characteristically do so in the lung without involving the liver and spleen as well. Much information can be gotten from cultures and staining of the tissue for various bacteria. Aerobic and anaerobic cultures from the lung revealed only staphylococci and Vincent's organisms. Culture of splenic tissues, carried out under increased carbon dioxide tension in an

attempt to recover brucella organisms, was negative. Sections of the lungs stained from bacteria again showed only gram-positive cocci and the Vincent's fusiform organisms and the staphylococci which are present are not intimately associated with the lesions which you have seen. Dr. Parker Beamer searched suitably stained sections for tubercle bacilli for hours and was unable to find any. Likewise, no fungi could be demonstrated and none were recovered on culture on Sabouraud's medium.

We next turn to a consideration of physical agents which might have been responsible for the changes seen here. Radiant energy may be ruled out by the fact that the lesion was obviously present before the radiation therapy had been given and the changes are not typically those seen within three months of the date of exposure to roentgen rays. Let us then turn to the problem of the fat-containing macrophages. The amount of fat present is greatly out of proportion to the amount which would be expected in simple organizing pneumonia or a destructive process in the lungs *per se*. It is true that fat accumulates in any inflammatory process in which tissue has been destroyed, but there is not sufficient destruction here to explain the great number of fat-containing macrophages. We therefore come to the possibility that the patient had lipid pneumonia as suggested by Dr. Goldman. The pathologic changes are entirely consistent with that diagnosis if one makes the assumption that the lipid which was introduced into the lung was a saponifiable fat from which fatty acids could have been liberated. It is not characteristically the type of lipid pneumonia seen with a non-saponifiable fat such as mineral oil for the latter accumulates in large

droplets, there is more fibrosis and fatty macrophages are not seen. However, if the fat is saponifiable, this represents a typical clinical picture. I can think of no other possible explanation. In an attempt to substantiate the diagnosis we contacted various physicians in other cities who had taken care of this patient. Several stated, "Yes, this patient had used a large amount of some type of nose drops but I do not know their nature because they were purchased by her at a drugstore without a prescription."

DR. ALEXANDER: Is there any possibility that this woman had fat embolism at the time of injection of the estrogenic substances?

DR. R. A. MOORE: I think the amount of fat present is much too great for that.

DR. ALEXANDER: I would like to ask Dr. Goldman if one may find fat in the sputum by proper staining.

DR. GOLDMAN: I believe there are several cases on record in which that was done.

DR. R. A. MOORE: This diagnosis could possibly have been made clinically if the sputum had been stained for fat.

Final Anatomic Diagnoses: Lipoid pneumonia of all lobes of the lungs with organization and necrosis (presumably caused by a saponifiable fat); fibrous pleural adhesions, bilateral; pleural effusion, serosanguineous fluid (right 100 cc.; left 500 cc.); atrophy of the spleen; central necrosis of liver; acute erosions of the gastric mucosa.

Bacteriology: Lung, aerobic: (pure culture) hemolytic *Staph. Aureus*. Spleen, no growth aerobically, anaerobically or under increased CO₂ tension.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Complete Heart Block in a Case of Pregnancy*

ROBERT M. BARTON, M.D. and CHARLES N. LADUE, M.D.

Dallas, Texas

THE historical record of the disorder we now recognize as complete heart block is of interest in that Morgagni recorded the first case of heart block in the year 1761, but it was nearly a century later before clinical accounts of this disorder were published by Robert Adams and William Stokes.¹ In 1893, His contributed immeasurably to the understanding of heart block and in 1903 Von Stark² called attention to the fact that complete heart block could occur on the basis of a congenital defect in the conduction system.

In the early part of the present century clinicians became more interested in recognizing and reporting cases of congenital complete heart block, and in 1920 Carter and Howland³ reviewed seven established cases and added one of their own. Yater² in 1929 reported a case of an infant whose heart beat two weeks before birth was found to be slower than the mother's heart rate. This child died soon after birth and at autopsy several congenital anomalies were found including complete situs inversus. On dissection the A.V. node was found to be completely separated from the A.V. bundle.

Yater et al.,⁴ in 1933, reported another case of an infant with complete congenital heart block. The autopsy on this patient revealed a defect in the interventricular septum and almost complete absence of the bundle of His. These authors deemed it

necessary to proclaim certain criteria for the proper diagnosis of congenital complete heart block and their standards were: (1) bradycardia which must have been noted at an early age; (2) no history of infection such as diphtheria, rheumatic fever, chorea or congenital lues which might have caused the heart block, and finally (3) proof by graphic means. The additional signs which add weight to the diagnosis of this disorder are the occurrence of syncopal attacks at an early age and evidence of definite features of congenital heart disease. The authors also assert that the causes of congenital complete heart block are: (1) developmental defect of the bundle of His; (2) prenatal endomyocarditis and (3) congenital lues with involvement of the bundle of His.

In 1934, Yater, Leaman and Cornell⁵ reported the third case of congenital complete heart block studied by serial section through the conduction system. This patient was an infant who was cyanotic at birth and was found to have a complete heart block with a rate of 40 as confirmed by electrocardiogram. The patient expired after eighteen hours and autopsy disclosed an interauricular septal defect, a marked defect of the interventricular septum and a lack of continuity between the bundle of His and the A.V. node.

Campbell and Suzman⁶ reported on eight cases and emphasized that the disorder

* From the Department of Medicine, School of Medicine of the Southwestern Medical Foundation. Read before the Texas State Heart Association, May 6, 1945.

of complete congenital heart block is more common than previously considered. The ventricular rate in their patients ranged from 42 to 56 and quickened to 60 or faster on exercise. The authors observed an Adams-Stokes seizure in one of their eight patients. They emphasized that frequently there was some degree of patency of the interventricular septum and usually a prominence of the pulmonary conus. It was the opinion of these authors that the prognosis in such cases was usually good if the associated malformation was not serious. They concluded that the congenital malformation and not the complete heart block is the determining factor in the prognosis and they reiterate that heart block itself may be compatible with a perfectly normal life.

Wenner⁷ in 1944 called attention to the eighty-five authentic cases of congenital complete heart block that have been reported and added another. This author pointed out that clinical signs of congenital heart disease and syncope attacks in young children are valuable evidence of the congenital nature of the block. He also observed that an interventricular septal defect is the most common lesion noted. Wallgren and Windblad⁸ found signs of this defect in fifty-one of the seventy-seven cases they reviewed, and in addition, a large number of these patients had other associated anomalies such as pulmonary artery stenosis, patent ductus arteriosus and dextrocardia. In six of eleven patients examined at autopsy definite information concerning the conduction system was found. A break in the system was noted most often just below the A.V. node and in four patients there was severing of the bundle of His by fibrous tissue; "a developmental disunity in the tissues of the conduction system."

There are a number of interesting and useful clinical facts to be derived from the accounts of congenital complete heart block as reported in American literature.

In the cases reviewed by Yater and others it was found that syncope was not infrequent and cyanosis was observed in approximately one-half of the patients. On the other hand, dyspnea and evidence of congestive failure was conspicuously absent. The pulse rate was rarely under 40, usually being in the range of 50 or higher. The blood pressure was elevated in a few of the reported cases and ranged from 150 to 190 systolic and 90 to 100 diastolic. The A.V. block has been found to be partial or complete. A large number of patients followed have expired in early life and death was usually due to other malformations and not to the congenital heart block; however, the frequency of Adams-Stokes seizures in some patients increases the tendency to sudden death. In spite of many handicaps associated with congenital heart block there are patients who not infrequently survive to adult life and beyond. It has been generally observed that faulty growth may be present and stigmas such as club fingers are not uncommon.

As to the frequency of complete heart block in general, it was found to be present in only 108 cases of a total number of 13,211 cardiac cases studied by White,⁹ Lemann,¹⁰ Sprague¹¹ and others. White estimated that 90 per cent of the higher grades of heart block occurred in patients over fifty years of age. Of 10,000 patients studied at the Massachusetts General Hospital upon whom electrocardiograms were taken, there were only four patients who had complete heart block thought to be on a congenital basis.¹²

Mitchell et al.,¹² reviewed 17,862 deliveries at the Kings County Hospital during a five year period and found that there had been only one patient who had manifestations of complete heart block. These authors considered this patient to have a congenital type of heart block and stated that most patients with heart block who become preg-

nant have a congenital anomaly as the basis for the conduction defect.

When one considers the above figures it seems obvious that pregnancy will occur rarely in an already relatively rare condition. Walz¹³ in 1922 reported the third authentic case of pregnancy in a patient with congenital complete heart block. In 1930, Herrmann and King¹⁴ described a patient who had complete A.V. block since the age of twenty and a record of six successful deliveries without complications. The heart block in this patient was thought to be on the basis of rheumatic fever.

Bernstein¹⁵ reviewed the literature up to January 1, 1936, and found only six recorded cases of complete heart block in which pregnancy with successful delivery had occurred. Bernstein reported a case of a twenty-three year old primipara, who after thirty-six hours in labor without progress, was subjected to cesarean section under local anesthesia. The puerperium was uneventful. The patient was found to have serologic evidence of syphilis and the cardiac lesion was ascribed to this etiologic agent.

Jensen¹³ states in his text, 1938, that sixteen other cases have been published in some detail and Nest¹³ mentioned three additional case reports. There have been other reports¹⁶ from time to time, bringing the total up to approximately twenty-six.

Mitchell et al.,¹² in 1943, reported a case from the Kings County Hospital of a twenty-three year old primipara with complete congenital heart block who experienced normal pregnancy, normal delivery and uneventful recovery. The heart block in this patient was present one year later. Mitchell,¹² Bernstein¹⁵ and others have emphasized that the prognosis in these cases is good because the myocardium is unimpaired. It is the opinion of these writers and of most investigators that delivery should be as usual and that interruption of pregnancy and sterilization procedures are not justified.

CASE REPORT

A twenty-one year old, white housewife was seen on September 17, 1940, because of an acute respiratory infection. She had been healthy all her life and had experienced only the usual childhood diseases, with an occasional sore throat. At the age of eleven she had an episode of tonsillitis which kept her in bed for approximately one week. She returned to school and her dancing lessons and recalled no unusual fatigue. She became an acrobatic dancer and had never experienced unusual breathlessness or fainting. Menarche was established at the age of thirteen and was regarded as of normal pattern. During her second or third year of college, at about the age of seventeen or eighteen, the school physician remarked that her pulse was slow. She continued active physical exercises and acrobatic dancing. At eighteen her appendix was removed and at the age of nineteen a tonsillectomy was done.

Her height was 5 feet 5 inches and she weighed 116 pounds. She was well developed and except for the findings referable to her heart, physical examination revealed no abnormalities. The apex beat was in normal location and no thrill was felt. Percussion of the heart borders disclosed no enlargement. A soft systolic murmur was heard over the entire precordium, most distinctly over the third left rib near the sternum. Her pulse rate was in the forties. Auricular contractions were audible between ventricular systoles. Her blood pressure was 110 systolic and 70 diastolic. Blood studies were normal. Urinalysis and serology were entirely normal. An electrocardiogram revealed complete A.V. dissociation. Auricular rate varied between 72 to 82, while the ventricular rate was 52 to 64. The QRS complexes were normal and there was a normal axis deviation. T waves were positive in lead I, negative in leads II, III and IVF.

At the age of twenty-two she became pregnant. She progressed with no more than the usual discomfort and at term, after twelve hours labor, was delivered of a 6½ pound normal infant. At the height of labor, her pulse had increased to 64 but later this promptly subsided to the high forties where it remained during an uneventful puerperium.

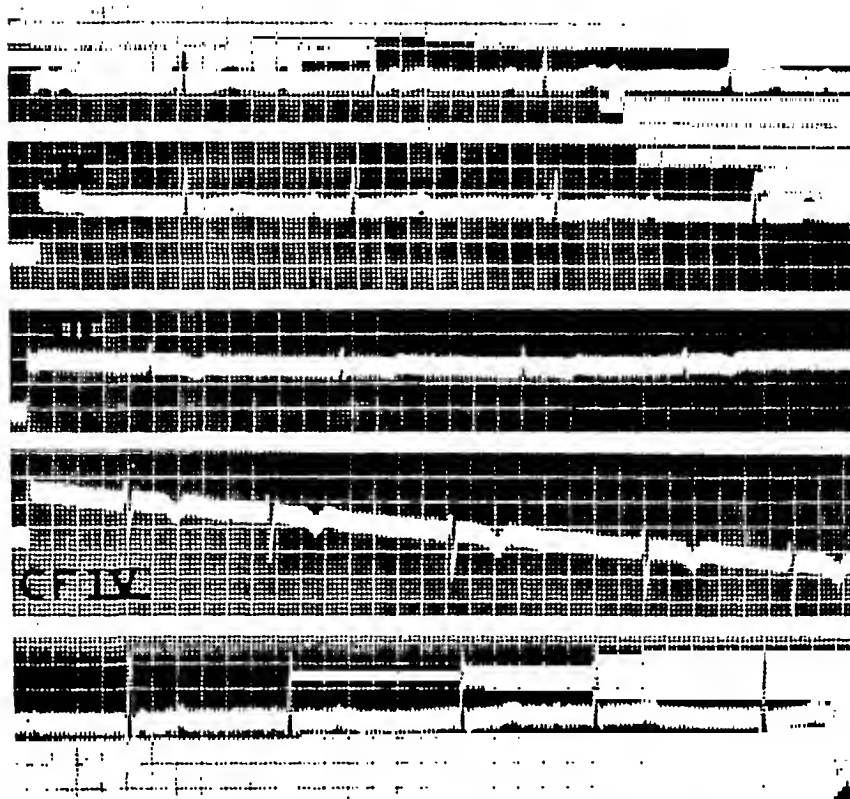


FIG. 1. Electrocardiogram, December 12, 1945, showing complete A.V. dissociation.

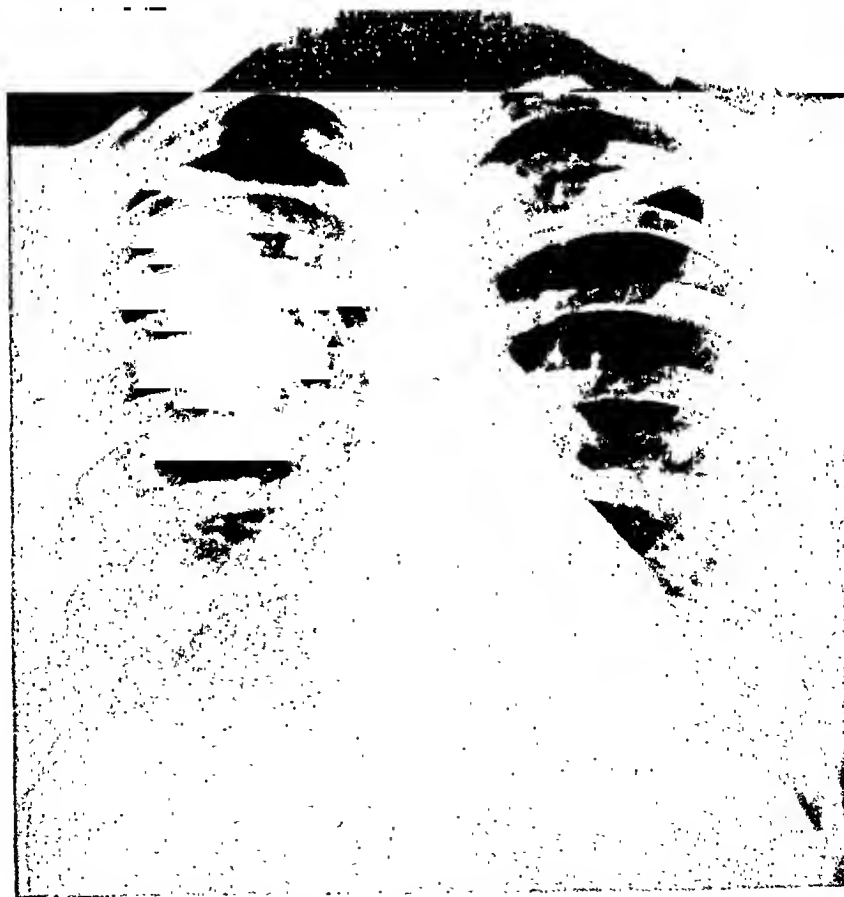


FIG. 2. Teleroentgenogram showing slight generalized enlargement of heart.

She has remained in good health and was recently seen in the eighth month of her second pregnancy. A recent teleroentgenogram showed a slight enlargement of the right and left ventricle. Subsequent electrocardiograms have continued to show 2 to 1 A.V. dissociation. An ECG taken on December 12, 1945, demonstrated an auricular rate of 64 to 66 with a ventricular rate of 40 to 42. The T waves were negative in leads III and CFIV.

While one might question this case as satisfying all of Yater's criteria for congenital block (a slow pulse was not discovered until she was seventeen or eighteen years of age) we think it fits that classification. An illness at eleven years of age was present; however, the patient recalls promptly returning to school without a period of convalescence. We doubt that she suffered an endomyocarditis at this time and recovered so completely and promptly. The systolic murmur probably represents an interventricular septal defect. We believe this to be a case of congenital complete heart block in a patient who experienced normal pregnancy, uncomplicated delivery and uneventful recovery.*

SUMMARY

In summary we wish to emphasize the relatively infrequent occurrence of acceptable cases of congenital complete heart block as reported in American literature. A review of the literature reveals that only twenty-six cases of complete heart block in pregnant women have been reported.

A report of a patient with congenital complete heart block who experienced normal pregnancy and uneventful recovery has been presented. This report adds emphasis to the current belief that patients with complete heart block who become pregnant should be allowed to continue a normal pregnancy, provided that the asso-

ciated congenital defects do not constitute an indication for therapeutic abortion.

It is our hope that the report of this case of congenital complete heart block in pregnancy may stimulate interest in this rare condition and ultimately lead to better understanding and proper recognition of this entity.

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* Since this paper was delivered, this patient, on July 16, 1946, delivered a healthy 7 lb. male infant. Convalescence was uneventful.

Southern Society for Clinical Research

SECOND ANNUAL MEETING, NEW ORLEANS, JANUARY, 1948

Presidential Address

The Middle Zone in Medicine

TINSLEY R. HARRISON, M.D.*

Dallas, Texas

IF one were still young enough to be valorous, a presidential address would offer the chance to illustrate the dictum that "young men are fitter to invent than to judge, . . . fitter for new projects than for settled business," and to present a scientific discussion of recent investigative work. One old enough to be discreet would probably make no speech at all, realizing that "even a fool, when he holdeth his peace, is counted wise." He who, like myself, is neither young enough to retain valor nor yet old enough to have achieved discretion, will be tempted to philosophic discourse and, pretending to disdain both the hectic energy of youth (as Brownian movement) and the professorial calm of age (as atrophy of imagination), will discuss "Whither are we tending?" and "the evils of the times" as though endowed with an understanding which he has not.

The remarks to follow are directed toward all of us who teach clinical medicine, and are based on the belief that in many of our better schools research is outstripping teaching, and are for the purpose of urging that we preach what we practice. This Phillipic (without eloquence) is therefore aimed at the general concepts of disease which we allow to develop in the minds of our pupils.

To say that most of our progress during the nineteenth century, and much of it in the twentieth, developed from the deadhouse and hence originally stems from the ancient Egyptian embalmers is to state a truism. It is equally trite to point out that much of our progress in recent years has come from a better understanding of the rôle of emotional disturbances in the production of symptoms, and hence may be traced back to primitive man and his concepts of infestation by evil spirits. Clinical teaching of

today is often based largely on the assumption that patients either have, on the one hand, demonstrable structural disease or, on the other hand, functional disorders dependent on emotional disturbances. Many of our able clinicians, failing to find an organic ailment and observing that the patient is somewhat anxious and disturbed (as most patients are), refer the problem to the psychiatrist, acting on the principle that "words are the physicians of a mind diseased." Any lingering doubts based on some subconscious dissatisfaction with either the structural or emotional interpretation of the nature of the symptoms are likely to be met by adding the label "psychosomatic," without pausing to consider that a name does not necessarily constitute an explanation and that a useful concept deserves a better fate than to become a scrap basket for our ignorance.

It is my opinion that such a conception of the causation of symptoms is accurate in so far as it goes but is decidedly incomplete, and that when we practice it with our patients or foster it in our students we err in the sense that "a wrong doer is often a man that has left something undone, not always he that has done something." One does not have to be a Prometheus to have his liver picked at; and at the risk of exposing mine to the onslaughts, not of vultures, but of more predatory birds (pathologists and psychiatrists), I wish to urge that our clinical stool have a third leg, without which the other two are often as useless as Icarian wings that melt in the sun.

One objection to the structural-emotional dualistic conception of the cause of symptoms is its relative therapeutic nihilism. A large proportion of structural disorders are irreversible, at least at the present time. Some few emotional

* From the Southwestern Medical College, Dallas, Texas.

ills are irreversible; more can be successfully treated, but many of these can be expected to respond only to prolonged and necessarily expensive psychotherapy.

A more compelling objection to this dualistic concept is its failure to account for the symptoms in a large proportion of our patients. Abdominal pain will serve as an apt illustration. The most common cause of this symptom is neither structural disorder nor emotional upset but quantitative or qualitative dietary indiscretion. Such common and important causes of abdominal discomfort as acute appendicitis and friction with in-laws are less frequent than being "crammed with distressful bread," while peptic ulcer and trouble with the boss assume secondary rank when compared with the ingestion of one man's poison which is another man's meat. Such abdominal pains are neither emotional nor structural; they belong to the middle zone of somatic functional disorders.

To illustrate this thesis with other common symptoms we may consider syncope and faintness. The most frequent causes of these symptoms are not such structural disorders as cerebral neoplasm or islet cell tumors, nor yet such a common emotional disturbance as vasovagal syncope, but rather the non-psychogenic functional group of disorders such as idiopathic epilepsy, carotid sinus syncope, paroxysmal tachycardia, postural hypotension resulting from prolonged bed rest and hypoglycemia consequent to faulty dietary habits. Here again, among the most common causes of important symptoms we have conditions which can neither be assigned to the realm of an emotional Ariel nor to the kingdom of a structural Caliban; they belong to the middle zone.

The point at issue may perhaps be strengthened by citing a specific case: A thirty-seven year old woman developed recurrent headaches of increasing frequency and severity. These began a few months after the death of a brother to whom she was devoted. After several weeks the seizures were complicated by the presence of outspoken vertigo. Examination revealed unilateral impairment of hearing and evidence of depression which the patient attributed to the headaches. She was seen by several internists, an otolaryngologist, a neurologist, a neurosurgeon, an allergist and a psychiatrist, all of whom were unusually competent. Opinions were divided as to whether cerebral neoplasm or emotional disturbance was the cause of the

symptoms. As a temporizing measure she was given a trial on elimination diets which she followed carefully, except for continuing to take coffee of which she was very fond. The symptoms continued. Several weeks later coffee was withdrawn and all manifestations except the deafness abruptly ceased. After seven years of complete freedom from headache the patient drank two cups of coffee at about 10 A.M. At 6 P.M. a severe headache set in. Ergotamine produced prompt relief of the headache but after about one-half hour severe substernal pain associated with fear of impending death occurred. When she was seen an hour later by two physicians, the possibilities of myocardial infarction and of an anxiety reaction were considered. In the light of the possibility that the pain might conceivably be the result of coronary constriction, induced by ergotamine, nitroglycerine was administered. Within five minutes the pain and anxiety were completely relieved and have not recurred, despite vigorous physical exertion and considerable emotional stress.

This patient had at different times two symptoms: headache and constrictive chest pain which could readily have been ascribed either to structural disorder or to emotional disturbances. In both instances non-psychogenic functional disorders were responsible.

Those of you with an historical bent, mindful of my present abode, will naturally wonder what the shooting is about, while those with literary inclinations may be tempted to reflect that the most popular Elizabethan drama in the most spacious state is "Much Ado about Nothing," and all of you may agree that there can be little significance in emphasizing something which we all practice daily in our investigative work, namely, the study of the somatic mechanisms involved in the production of symptoms. Actually, we often do not preach that which we practice. Since the application of chemistry and physics to the study of disease is a relatively new phenomenon, we cannot expect the middle-aged physician to be steeped in this "physiolo-somatic" approach to disease. However, when our recent graduates and students persist in the dualistic structural and emotional approach and display, as nearly all do, no evidence of understanding the middle zone of non-psychogenic functional disorders as the third and often most important leg of the stool, one is forced to conclude that we who teach clinical medicine, and who are far from ignorant of the significance

of this group of disorders, are failing to impress such knowledge upon the minds of our students. It would seem to be the special function of those who teach internal medicine and pediatrics to temper alike the harsh structural winds of pathology and surgery and the soft seductive emotional zephyrs of psychiatry, with the cool, clean air of clinical physiology if a healthy intellectual climate is to be achieved for our pupils.

It has already been stated that the modern concept of the great importance of emotional conflicts as causes of symptoms may be considered as having been derived from primitive man and his concern with evil spirits, while the structural approach to disease can be traced via the dead house to the early Egyptian embalmers. In emphasizing the middle zone are we forsaking history for hysteria, or can we assign to this concept also a respectably ancient origin? One need not seek far to find that the clearest thinkers of antiquity, the Greeks, were reasoning in such terms when they ascribed disease to disturbances in the four humors, a concept of disease which is based neither on structural change nor on emotional disturbance but

rather on the middle zone of nonpsychogenic functional disorders. These several ancient approaches, each containing a germ of truth, are separately inadequate, but when integrated furnish a firm basis for clinical thinking. To provide such a synthesis is one of the chief tasks of modern clinical teaching. Such teaching, like any other, can be effective only if it stems from example. If we wish our pupils to study the known, we, their teachers, must light their paths by studying the unknown. A society such as this one may, over the long pull, actually accomplish as much good through its inevitable by-product, better teaching, as through its immediate objective, the encouragement of research. In furnishing such encouragement we shall refuse to allow the shocking results of the recent advances in nuclear physics to force us to accept the ecclesiastic proverb that "He that increaseth knowledge increaseth sorrow," but shall adopt a long-term viewpoint and, endorsing that fermentative spirit which is a prerequisite for research, follow the prophecy of Daniel that, "Many shall run to-and-fro and knowledge shall be increased."

Abstracts of Southern Society for Clinical Research

SECOND ANNUAL MEETING, NEW ORLEANS, JANUARY, 1948

PROCEEDINGS

(Read by presentation)

1. HYPOKALEMIA MASKING THE SYMPTOMS OF HYPOCALCEMIA

FRANK L. ENGEL, M.D. *and (by invitation)*
SAMUEL P. MARTIN, M.D.

From the Department of Medicine, Duke University
School of Medicine, Durham, N. C.

(We are indebted to Dr. H. M. Taylor of the Department
of Biochemistry for the chemical analyses
in this study.)

Two patients with hypocalcemia and hypokalemia due to chronic diarrhea, one complicated by diabetic coma, have been observed. One suffered from non-tropical sprue, the other from probable pancreatic insufficiency. Both were observed clinically during periods in which they exhibited preëminently hypocalcemic tetany or hypokalemic paresis. During both phases the serum calcium was consistently below 6.5 mg. per cent but tetany was apparent only when the serum potassium was above approximately 2.5 mEq/L. Paresis appeared at the same Ca levels when the potassium fell below approximately 2.0 mEq/L. In one patient simultaneous measurements of serum calcium and potassium, electrocardiograms and studies of nerve-muscle irritability were carried out during intravenous administration of potassium and calcium salts. During the hypocalcemic-hypokalemic phase with paresis administration of potassium produced a decrease in chronaxie with marked clinical signs of tetany as the serum potassium rose, the serum calcium remaining relatively constant. These effects were reversed either by the spontaneous decline in potassium after discontinuing infusion or by administration of calcium before potassium levels had fallen to the initial low level. Measurements of serum sodium, chloride, CO₂ combining power, phosphate, total protein, albumin and globulin were made at appropriate intervals. These data suggest that

potassium depletion may be a reason for the not infrequent failure to develop clinical tetany despite hypocalcemia in steatorrhea and emphasize the need for caution in treating this hypokalemic syndrome with intravenous potassium salts.

2. STUDIES ON DICUMAROL IN HUMAN BEINGS; ITS NEUTRALIZATION BY VITAMIN K₁ OXIDE, MENADIONE BISULFITE, SYN-KAYVITE AND BLOOD

DAVID F. JAMES, M.D., IVAN L. BENNETT, JR.,
M.D., PERITZ SCHEINBERG, M.D. *and* JOHN J.
BUTLER, M.D. (*introduced by* Arthur J.
Merrill, M.D.)

From the Department of Medicine, Emory University
School of Medicine, Atlanta, Ga.

The impression that dicumarol toxicity can readily and consistently be controlled by the intravenous administration of 64 mg. menadione bisulfite is widespread but based on a relatively small number of reported observations. In order to establish a broader clinical basis for the control of dicumarol action, menadione bisulfite in 64 mg. and larger amounts were given to patients whose prothrombin times were prolonged by dicumarol to within the range where spontaneous bleeding has been noted. The action of menadione bisulfite was compared with that of vitamin K₁ oxide, synkayvite and fresh and bank blood.

One hundred one patients were given dicumarol in the usual dosage. When the prothrombin time exceeded that of control plasma diluted to a concentration of 20 per cent, the patient was either allowed to return untreated to his normal prothrombin level or was given large single doses of the substances mentioned above. Blood samples taken at frequent intervals during the succeeding twenty-four hours, and daily thereafter, were studied for prothrombin activity.

Vitamin K₁ oxide was markedly superior to the other substances tested. The prothrombin time of patients given 0.5 Gm. or more of this material intravenously required an average time of thirteen hours to arrive and stay within safe limits (i.e., at thirteen hours the patient's prothrombin time was as short as or shorter than that of 30 per cent normal control plasma).

3. EFFECT OF COMBINING VASOCONSTRICTORS WITH LOCAL ANESTHETICS UPON THE DURATION OF SPINAL ANESTHESIA IN MAN

KENNETH BRAY, M.D., S. KATZ, M.D. (*by invitation*)
and J. ADRIANI, M.D.

From the Department of Surgery, Louisiana State University School of Medicine, New Orleans, La.

The usefulness of epinephrine in prolonging the action of local anesthetics for infiltration, nerve block and topical use has been established. Relatively speaking, other vasoconstrictors are nowhere as effective. The usefulness of epinephrine intrathecally is not accepted, as its effectiveness is controversial. Recent reports based mostly upon clinical impression have added confusion to the issue and no controlled studies are available in man.

In this study patients requiring spinal anesthesia four and five times in succession were used. Three hundred observations were made using a short acting drug (procaine), an intermediate acting preparation (pontocaine) and a long acting drug (nupercaine) alone, twice in succession. In subsequent administrations the effect of adding epinephrine, ephedrine and neosynephrine upon intensity and duration of action were compared with results in the controls.

4. URECHOLINE IN THE TREATMENT OF MOTOR ABNORMALITIES IN THE GASTROINTESTINAL TRACT OF NEUROGENIC ORIGIN

R. W. RUNDLES, M.D. and GEORGE J. BAYLIN, M.D. (*introduced by Eugene A. Stead, Jr., M.D.*)

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

Gastric dilatation with prolonged retention of food and secretion has been a major post-operative complication of vagotomy. Twenty-two patients with this complication were treated with urecholine (urethane of B-methylcholine chloride). Of the parasympatheticomimetic drugs urecholine appears to be the most effective

as well as least likely to cause side reactions. Within three to five minutes after hypodermic injection of 5 mg. of the drug, vigorous peristaltic activity developed and was usually effective in emptying the stomach. Oral administration of the drug in doses of 10 to 50 mg. was effective in some patients. Transit of barium through the jejunum was hastened, the caliber of the intestine decreased and mucosal pattern became less coarse.

Disorganized gastrointestinal activity with gastric retention in spite of free passage of barium into the upper intestinal loops occurs in some patients with diabetic neuropathy. In three such patients urecholine was effective in promoting gastric emptying and restoring normal intestinal motility as judged roentgenologically and by disappearance of clinical symptoms.

Three patients with megacolon were treated with oral doses of urecholine for periods of eight to twelve months. Bowel habits became normal and there was complete freedom from clinical symptoms.

5. CLINICAL DESCRIPTION AND CHEMICAL PATHOLOGY OF THE SYNDROME OF FAMILIAL IDIOPATHIC DYSPROTEINEMIA

F. HOMBURGER, M.D., N. F. YOUNG, M.D., MARY L. PETERMANN, M.D. and EDWARD C. REIFENSTEIN, JR., M.D.

From the Departments of Clinical Investigation and Protein Chemistry, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center, New York, N. Y.

Four of six members of one generation in the same family were found to have an abnormal distribution of protein components in the blood plasma; although only two of the four had gross hypoproteinemia, all four had clinical manifestations, particularly edema. In the females the dynamics of peripheral circulation were disturbed. Detailed studies have eliminated the usual causes of disturbances of the circulating protein components. Electrophoretic, immunologic and chemical studies of the plasma proteins were undertaken in an effort to clarify the pathogenesis of this disturbance. Data will be reported on the rate of disappearance of circulating injected human albumin and the rate of restoration of circulating protein following plasmapheresis. The significance of some of the findings will be discussed.

6. ASPECTS OF THE BIOLOGIC DECAY PERIODS OF SODIUM IN NORMAL AND DISEASED MAN

SAM THREEFOOT, M.D., (*by invitation*), GEORGE BURCH, M.D. and (*by invitation*) PAUL REASER, M.D.

From the Department of Medicine, Tulane Medical School and Charity Hospital, New Orleans, La. (Aided by a grant from the Life Insurance Medical Research Fund, the War Contract No. W-49-007-MD-389, the Helis Institute for Medical Research and the Mrs. E. J. Caire Fund for Research in Heart Disease.)

A knowledge of the duration of time for which a radioactive element is retained in the body has important significance physiologically in safety considerations and in dosage calculations in tracer studies and isotope radiation therapy. The biologic decay-life of sodium in man can be determined satisfactorily with the long half-life Na^{22} ($T_{1/2} = 3$ yr.) but not with Na^{24} ($T_{1/2} = 14.8$ hr.). During the course of experiments Na^{22} , with an activity of such that 10,000,000 to 17,725,000 disintegrations occurred per minute, was injected into each subject. A daily blood serum concentration of Na^{22} was determined for from thirty to sixty consecutive days. All samples of urine were collected separately and the Na^{22} excretion determined for each. The subjects consisted of four control subjects free from cardiovascular and renal disease, six subjects with chronic congestive heart failure (two were slowly improving, two rapidly improving and two becoming worse) and two subjects with chronic glomerulonephritis of the nephrotic type.

Since only the serum concentration of Na^{22} and the rate of urine excretion of the radioelement were measured, it was not possible to know the time required to excrete one-half of the injected Na^{22} , the biologic half-life period ($B_{1/2}$), *per se*. Therefore, it was necessary to introduce the following terms:

- (1) $C_{1/2}$ = time required to reduce the serum concentration to one-half the value obtained at any time after equilibrium between the Na^{22} and Na^{23} of the body has been reached.
- (2) $U_{1/2}$ = time that would be required to eliminate in the urine one-half of the administered Na^{22} .

The results are briefly summarized by Table 1. It can be seen that with the exception of Subject No. 2 the $C_{1/2}$ periods were less than the $U_{1/2}$

ones. This is to be expected because of the influence of other factors, such as other avenues of sodium excretion, shifts of sodium within the sodium compartments of the body and variations in the volume of these compartments. The subjects with chronic congestive heart failure

TABLE 1
CONTROL

Subject No.	$C_{1/2}$	$U_{1/2}$	Days of Continuous Observation	Weight Change (Pounds)
1	14	30	62	- 3.5
2	13	9	22	-14
3	12	42	45	-11
4	14	34	65	+ 2.3
Mean	13.3	28.8	48.5	- 6.6

Congestive Heart Failure
(Slowly Improving)

5	40	60	35	-18
6	42	72	46	- 7
Mean	41	66	40.5	-12.5

Congestive Heart Failure
(Rapidly Improving)

7	13	26	62	-29
8	28	33	58	-17
Mean	20.5	29.5	60	-23

Congestive Heart Failure
(Slowly Becoming Worse)

9	24	72	68	+17
10	30	48	58	- 5.5
Mean	27	60	63	+ 5.8

Chronic Glomerular Nephritis
(Nephrotic Type)

11	58	660	45	+15
12	54	366	71	-86
Mean	56	513	58	-35.5

Summary of Results. The $C_{1/2}$ value indicates time in days required for the serum Na^{22} concentration to reach one-half the initial equilibrium concentration. The $U_{1/2}$ values represent the time in days required for one-half of the total Na^{22} injected to be eliminated by the urine.

and those with chronic glomerulonephritis of the nephrotic type had $C_{1/2}$ and $U_{1/2}$ periods which were longer than those of the controls. (Table 1.) Sodium and water diuresis in the

subjects whose congestive heart failure rapidly improved resulted in a definite shortening of the $C\frac{1}{2}$ and $U\frac{1}{2}$ periods, the times becoming even less than that for the normal subjects on high sodium intake. The $C\frac{1}{2}$ periods in the control subjects were essentially the $B\frac{1}{2}$ periods. This is less likely to be true for the abnormal subjects.

The $C\frac{1}{2}$ and $U\frac{1}{2}$ periods were affected by measures which influenced sodium metabolism and excretion such as sodium intake, desoxycorticosterone acetate, mercurial diuretics, water intake, pitressin and others.

These experiments have shown that the $B\frac{1}{2}$ as well as the $C\frac{1}{2}$ and $U\frac{1}{2}$ for sodium are quite variable, being influenced not only by normal physiologic phenomena but particularly by disease and drugs. These variations must be taken into consideration when calculating the safety doses for radiosodium. $C\frac{1}{2}$ and $U\frac{1}{2}$ periods found for Na^{22} indicate the length of time required to turnover Na^{23} in men. These experiments will be published in detail elsewhere.

7. URINARY THYROTROPIC HORMONE AS A DIAGNOSTIC TEST IN PRIMARY HYPOTHYROIDISM AND IN EVALUATION OF THERAPY IN DISEASES OF THE THYROID GLAND—A PRELIMINARY REPORT

JAMES A. GREENE, M.D. (*by invitation*) DON W. CHAPMAN, M.D. and LYNN BERNARD, M.D.

From the Department of Medicine, Baylor University College of Medicine and Hermann Hospital, Houston, Texas.

The urinary thyrotropic hormone excretion has been ascertained in four cases of myxedema before thyroid therapy and in five before and following thyroid therapy for periods from six to eighteen months. In addition, the thyrotropic hormone excretion has been ascertained in the urine of nineteen patients with classic hyperthyroidism before therapy and in five of them following effective thiouracil therapy. The hormone assay was carried out according to the method of Parks and day old chicks were used as the test animal.

Active thyrotropic hormone was present in the urine in all subjects with myxedema before treatment and the amount diminished or disappeared following thyroid therapy. The active hormone was present in the urine of only one subject with hyperthyroidism before therapy and appeared in all patients following effective

treatment with thiouracil. The possible significance of these findings to the physiologic relationship of the thyroid and pituitary glands and their diagnostic and therapeutic evaluation will be discussed.

8. PTEROYLGLUTAMIC ACID BALANCE STUDIES ON MONKEYS

PAUL L. DAY, M.D. (*by invitation*) DOROTHY SUE GAINES, M.D., MARION MCKEE, M.D., PHYLLIS SCROGGIN, M.D. and RAYMOND HOUGHINS, M.D.

From the Department of Biochemistry, School of Medicine, University of Arkansas, Little Rock, Arkansas. (Aided by a grant from the Nutrition Foundation, Inc.)

Young rhesus monkeys were housed in individual steel metabolism cages and given a diet known to produce anemia, leucopenia and pteroylglutamic acid deficiency. The diet was supplemented with the amounts of PGA (pteroylglutamic acid) indicated below for periods of twenty-one to twenty-eight days. Daily urine and feces collections were made, and were analyzed for PGA using *Streptococcus faecalis*. When the diet was supplemented with 100 micrograms of PGA daily, the average daily output in micrograms was as follows: urine, 5.2; feces, 7.3; total, 12.5. When the daily dietary supplement of PGA was increased to 1 mg. the output in micrograms was: urine, 21.8; feces, 9.6; total 31.4. When the diet was supplemented with Difco yeast extract in an amount to furnish approximately 100 micrograms of PGA, largely in the form of PGA conjugate, preliminary data showed an output as follows: urine, 2.05; feces, 19.7; total 21.8. It is thus evident that when the level of intake of PGA is at the minimum daily requirement (100 micrograms) the total output in excreta is only about 12 per cent of the intake. A ten-fold increase in intake results in less than a threefold increase in output. Preliminary data indicate that the conjugate of PGA is not completely absorbed by the monkey.

9. TREATMENT OF NEOPLASMS BY THE DIRECT INFILTRATION OF RADIOACTIVE COLLOIDAL METALLIC GOLD

P. F. HAHN, M.D.

From the Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

Radioactive Au^{198} having a half-life of 2.7 days has a number of unique properties which

recommend it for use in tumor therapy. Having one of the best cross sections to thermal neutron flux, it is economically prepared in the uranium pile. The insolubility of colloidal metallic gold in body fluids enables one to set up millions of uniformly dispersed focal sources of beta radiation in discrete tumor masses or metastatic lesions causing a minimum of encroachment on neighboring normal structures in contrast to radiation from radium, radon or x-ray. Preliminary use in readily accessible tumors subject to follow-up inspection will be described. The potentialities in conjunction with surgery in the therapy of deep seated neoplasms will be considered. Present limiting factors in the exploitation of this valuable isotope are: (1) lack of knowledge of the various human tissue tolerances for beta radiation; (2) ignorance of various tumor sensitivities to this radiation and (3) relatively few experienced qualified investigators and therapists in this field.

10. FRACTIONATION AND CHEMICAL ANALYSES OF A MALIGNANT MOUSE THYMOMA

THOMAS N. WARREN, M.D. (*introduced by Alfred Chanutin, M.D.*)

From the Biochemical Laboratory, University of Virginia, Charlottesville, Va.

(This work was supported by a grant from the National Institute of Health and the National Cancer Institute.)

After subcutaneous transplantation of tumor cells into dba₂₁₂ mice, the animals survive about three weeks and shortly before death the tissue is grossly necrotic; at the end of two weeks this tumor is quite large and is classified as "healthy." The tumor tissue was treated so that (a) the stroma, (b) the tumor cells and (c) the cell-free saline extract were obtained. Each of these main fractions was further fractionated with the aid of ethanol and cold. All of the eleven subfractions were analyzed for total lipidic carbon, total cholesterol, total phospholipides, total nuclei acids and desoxyribonucleic acid.

Data will be presented for the fractions of fourteen-day ("healthy") and the twenty-day (necrotic) tumor tissues. The outstanding differences between these two groups are the decreased neutral fats or fatty acids and the increased total cholesterol in the necrotic tumor. Each subfraction has a characteristic and distinct chemical composition.

The data for the thymomas of mice treated with urethane and a nitrogen mustard and mice fed on a choline-enriched diet will be shown. The growth of the tumor at the end of twenty days in mice treated with urethane and HN2 was greatly inhibited, but the percentage concentrations of the various constituents were not markedly affected. Choline exerted very little effect on either the size or chemical composition.

From these data it would appear that the inhibition of tumor growth is not reflected by changes in the chemical composition of the tissue.

11. MORPHOLOGIC STUDIES IN SYPHILITIC LESIONS DURING THE HERXHEIMER REACTION

WALTER H. SHELDON, M.D. and ALBERT HEYMAN, M.D. (*introduced by Paul B. Beeson, M.D.*)

From the Departments of Pathology and Medicine of Grady Memorial Hospital and the Emory University School of Medicine, Atlanta, Ga.

The occurrence of the Herxheimer reaction in the treatment of syphilis has long been recognized but its mechanism has never been thoroughly investigated. Although the syphilitic lesions during this reaction frequently show gross changes, these have never been observed morphologically.

We have made histologic studies of the cutaneous and mucosal lesions during the Herxheimer reaction in series of patients with secondary syphilis. Definite morphologic changes occur during this reaction. They consist of congestion, edema, alteration of the vascular endothelium and acute inflammatory cell infiltration. These changes are confined strictly to the syphilitic lesions and disappear within six to eight hours. These histologic findings were observed in practically all patients with clinical evidence of the Herxheimer reaction. The same changes probably occur in the Herxheimer reaction of the cardiovascular and central nervous systems and may account for the serious clinical complications which are occasionally encountered.

Our studies suggest a similarity between the Herxheimer reaction and the tuberculin reaction and further investigation comparing these two phenomena may lead to a better understanding of some of the immunologic aspects of syphilitic infection.

12. EFFECT OF BENADRYL AND THOROTRAST ON EXPERIMENTAL ANAPHYLACTIC SHOCK

ANDRES GOTH, M.D. and JAMES HOLMAN, M.D.
(introduced by Arthur Grollman, M.D.)

From the Department of Pharmacology, Southwestern Medical College, Dallas, Texas.

The purpose of these experiments was to study the mechanism of the anaphylactic reaction and the site at which it takes place.

A series of twenty-one dogs were sensitized to horse serum. A few minutes prior to the shocking injection either benadryl—10 mg. per Kg.—or thorotrast—2 to 6 cc. per Kg—was injected intravenously. Five dogs received no pretreatment and served as controls. Blood pressure and clotting time were measured in all dogs before and after the shocking injection.

The results indicate that benadryl had only a slight effect in preventing the fall of blood pressure and it failed to prevent the incoagulability of the blood. On the other hand, large doses of thorotrast prevented both of these manifestations of anaphylactic shock.

These results can be best interpreted by saying that benadryl acts only as an antihistamine without affecting the fundamental process in the anaphylactic reaction, whereas thorotrast must have prevented the fundamental reaction from taking place. The latter drug could have accomplished this effect (a) by preventing the antigen from reaching the antibody or (b) by blocking the fundamental reaction which leads to the liberation of histamine and heparin. Since thorotrast is a powerful blocking agent of the reticulo-endothelial system the results of this study suggest that the reticulo-endothelial system plays an important rôle in anaphylactic shock.

13. RELATIONSHIP BETWEEN THE VALUE FOR THE RESTING CARDIAC OUTPUT AND THE SYMPTOMS OF CONGESTIVE HEART FAILURE

EUGENE A. STEAD, JR., M.D.

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.
(This work was supported by a grant from the Life Insurance Medical Research Fund.)

The relationship between the value for the resting cardiac output and the symptoms of con-

gestive heart failure is a complex one. Patients at the time of admission to the hospital will fall into the following groups:

1. Cardiac output low with failure and remains low with the disappearance of symptoms. Symptoms will be relieved by sodium restriction and continued use of diuretics. Majority of patients studied fall into this classification.

2. Cardiac output low with failure but increases with administration of digitalis or when complications such as pulmonary infarctions clear up; does not require salt restriction or diuretics when activity is reduced by bed rest.

3. Cardiac output normal with failure, remaining normal on compensation. Decomensation develops with increased activity. Cardiac output adequate at rest and symptoms at time of study present because of water-logging of the lungs which will persist until diuresis is completed.

4. Cardiac output high with failure, falls with compensation. This group includes: (1) restless, apprehensive, dyspneic patients whose outputs are adequate for rest but inadequate for mild exertion; (2) Patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi and certain infections.

14. RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND RENAL BLOOD FLOW

HAROLD D. GREEN, M.D. and (by invitation) BEN C. OGLE, M.D., J. MAXWELL LITTLE, M.D. WOODROW BATTEN, M.D., CARLOS RAPELA, M.D. (Rockefeller Foundation Fellow) and J. ROY HEGE, JR., M.D.

From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.
(Supported by a grant from Life Insurance Medical Research Fund.)

A kidney and the distal stumps of the aorta and vena cava were progressively dissected free from a dog (kidney dog) until they were connected only by the proximal portion of the aorta and vena cava. A donor dog was heparinized and its femoral artery connected with the distal stump of the kidney dog's aorta. The distal stump of the kidney dog's vena cava was connected with an outflow meter. The proximal

stumps of the kidney dog's aorta and vena cava were then ligated and severed, thus completing the isolation of the kidney without its being at any time subjected to ischemia. The perfusion pressure was varied by a suitable clamp on the femoral artery of the donor dog, the pressure being lowered for one-half to two minutes to a given level and then returned to the control pressure.

Control flows averaged 230 ml./min./100 Gm. of kidney (range 115 to 450) at arteriovenous differences of pressure of 120 mm. Hg.

Satisfactory plots of flow vs. A-V difference of pressure were obtained in seven experiments. Of these only one gave a curve concave to the pressure axis as described by Selkurt. Two were convex and the remainder were straight. All tended to intercept zero flow at approximately 20 mm. Hg pressure.

Conclusion. In the isolated kidney no evidence of autoregulation of flow was observed.

15. RELATIVE RATES OF RENAL EXCRETION OF SODIUM AND CHLORIDE IONS IN NORMAL, HYPERTENSIVE AND HEART FAILURE SUBJECTS

ANDREW J. CRUTCHFIELD, M.D. (*introduced by J. Edwin Wood, Jr., M.D.*)

From the University of Virginia School of Medicine, Charlottesville, Va.

Certain clinical and laboratory evidence suggests that renal retention of the sodium ion ranks among the primary events in the pathogenesis of the edema of congestive heart failure. The rôle of other extracellular electrolytes (e.g., chloride), though considered to be of lesser importance, has received little attention.

Experiments have been done in this laboratory to compare the relative rates of excretion of the sodium and chloride ions. The patients studied were grouped as follows: (1) normal, twenty-eight; (2) hypertensive without heart failure or clinical nephrosclerosis, eighteen and (3) edematous and non-edematous heart failure, twenty-five. The load of sodium chloride injected intravenously as 5 per cent solution actually contained 3,930 mg. of sodium and 6,070 mg. of chloride.

The average figures for the per cent of the load excreted over the five hour experiment period were as follows:

	Na Per Cent	Cl Per Cent
(1) Normal	20 1	19 2
(2) Hypertensive	19 2	19 4
(3) Heart Failure	9 0	10 1

These data indicate that the kidney of the heart failure patient excretes both sodium and chloride less rapidly than does the kidney of either the normal or hypertensive subject. Sodium excretion appears to be retarded slightly more than is chloride excretion although the difference is of doubtful significance.

About one third of the hypertensives had been treated for several months on low sodium diets similar to the ones used in treating the heart failure subjects. The normal sodium and chloride excretion by these subjects indicated that this type diet did not lead to body fluid deficit of either of these ions. It can safely be assumed, therefore, that the small excretion of sodium and chloride by the heart failure subject gave a true index of the existing renal ability to excrete these substances rather than indicating body fluid deficit of these substances.

16. EFFECT OF HUMAN SERUM ALBUMIN ON RENAL HEMODYNAMICS AND THE TUBULAR EXTRACTION OF PARA-AMINO HIP-PURIC ACID

WALTER H. CARGILL, M.D. (*introduced by Eugene A. Stead, Jr., M.D.*)

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

(This work was supported by grants from the Life Insurance Medical Research Fund and the Anna H. Hanes Fund.)

The intravenous administration of human serum albumin has been shown to produce a diuresis in patients with nephrosis. This has usually been attributed to a rise in plasma protein level and increased oncotic pressure of the blood. In an attempt to determine the immediate effect of albumin administration on the kidney, we have measured the inulin and para-amino hippuric acid clearance in two patients with nephrosis, five subjects with normal renal function, two hypertensives and one patient with subacute glomerulonephritis before, during and after the rapid intravenous administration of 300 cc. of a 25 per cent solution

of human serum albumin. In seven of these subjects the actual renal plasma flow was measured by the ratio

$$\frac{\text{PAH Excretion}}{\text{Arterial PAH conc.}-\text{Renal Venous PAH conc.}}$$

samples obtained from the right renal vein by catheterization being compared with simultaneous samples from the femoral artery.

The hematocrit fell in all subjects after albumin (average fall = 16 per cent of control) and the plasma protein concentration rose less than 1 Gm. per cent. In nine of the ten subjects an immediate increase in inulin (average rise 14 per cent) and PAH (average rise 37.4 per cent) clearances was found, with a fall in filtration fraction in every case. The PAH clearance was found not to be a valid measure of renal plasma flow, however, since the percentage extraction of PAH ($\frac{A_{\text{PAH}} - R_{\text{VPAH}}}{A_{\text{PAH}}}$) fell after albumin in each of the seven subjects in which it was measured (average fall = 19.6 per cent). The increase in actual renal plasma flow after albumin (average 44.3 per cent) was therefore greater than would be indicated by the PAH clearance (average 33.9 per cent) and the fall in filtration fraction correspondingly greater. In a control series of eight normal subjects under basal conditions consecutive determinations of renal PAH extraction at ten to fifteen minute intervals for one to two hours have shown a maximum variation of ± 1.8 per cent from the mean for each individual.

An immediate increase in urine flow in all subjects and in chloride excretion in the four subjects in which it was measured was found. The two patients with nephrosis differed from the others only in showing a greater rise in filtration rate and less fall in filtration fraction.

17. EFFECT OF SALINE CATHARSIS ON URINE SPECIFIC GRAVITY

PHILIP M. TILLER, JR., M.D. and ELLISON R. COOK, III, M.D.
(introduced by Thomas Findley, M.D.)

From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Methods used in concentration tests of kidney function fail to produce a consistent effect on urine specific gravity unless the subject has undergone water deprivation for at least twenty-

four hours. Even after such a long fast, wide variations have been observed in normal controls. A method capable of producing a consistent high elevation of urine specific gravity would be of value.

Observations of urine specific gravity have been made in normal subjects at fifteen minute intervals following administration of a sodium phosphate solution. In seven subjects the cathartic was administered thirty minutes after breakfast. Within two hours the mean urine specific gravity was 1.027. In eleven subjects the cathartic was given after an eight to twelve hour fast and the mean specific gravity in ninety minutes was 1.035, ranging from 1.030 to 1.039. In six series of observations in a single subject the urine specific gravity ranged from 1.034 to 1.039 at the end of 120 minutes.

It would seem that the rapid dehydration produced by saline catharsis is an effective means of increasing urine concentration and might prove a reliable test of renal function.

18. EFFECT OF ORAL STREPTOMYCIN AND PHTHALYLSULFATHIAZOLE ON BLOOD PHENOL CONCENTRATIONS AND SURVIVAL IN EXPERIMENTAL UREMIA

J. R. R. BOBB, M.D., STANLEY L. WALLACE, M.D. and J. MAXWELL LITTLE, M.D. (introduced by Harold D. Green, M.D.)

From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Blood phenol (tyrosine standard) determinations were made daily on five mongrel dogs. On the second day oral phthalylsulfathiazole (0.5 to 0.6 Gm./Kg. per day in divided doses) was started. On the fifth day bilateral nephrectomy was performed. The dogs died in from two to eight days postoperatively with phenol levels from 3.70 to 7.35 mg./100 cc.

A similar experiment was performed on four dogs using oral streptomycin* (0.48 Gm./day in divided doses). The dogs died two to three days postoperatively with phenol levels from 1.54 to 2.14 mg./100 cc.

On five control dogs blood phenol levels were determined for four days (1.05 to 2.19 mg./100 cc.). On the fifth day bilateral nephrectomy was done. These dogs died two to five days post-

* Kindly supplied by Dr. D. F. Robertson of Merck and Co., Inc.

operatively with determined phenol levels from 3.69 to 6.60 mg./100 cc.

Stool cultures showed that both drugs reduced gas-forming organisms.

There were no differences in the symptoms of uremia exhibited by the three groups of animals.

Conclusion. Intestinal organisms other than the coliform group were responsible for blood phenol production; blood phenol levels were of minor importance in producing the symptoms of experimental uremia.

19. STUDIES OF HUMAN CARBOHYDRATE METABOLISM BY THE LIVER CATHETERIZATION TECHNIC

PHILIP K. BONDY, M.D. and DAVID F. JAMES, M.D.
(introduced by Paul B. Beeson, M.D.)

From the Department of Medicine, Emory University
School of Medicine and the Medical Service,
Grady Hospital, Atlanta, Ga.

Animal experimentation has proved the importance of the liver in carbohydrate metabolism. Although clinical experience has tended to confirm in humans the findings of the physiologists in animals, direct observations relating to the rôle of the liver have not heretofore been possible in man.

By the use of the cardiac catheter technic one can obtain samples of blood from the hepatic veins. If simultaneous arterial and hepatic venous samples are analyzed for glucose, it is possible to determine whether the liver is extracting glucose from the circulation or breaking down glycogen to contribute glucose to the blood.

The data obtained show that under fasting conditions the human liver contributes glucose to the peripheral circulation. After the administration of glucose intravenously, the arterial glucose level exceeds the hepatic level, indicating that glucose is being stored. As the arterial glucose level drops, the hepatic venous level drops less rapidly until it again exceeds the arterial level, indicating that the liver is releasing glucose and "braking" the descending blood glucose curve.

When peripheral venous glucose levels are obtained, they are lower than the hepatic venous level at the peak of the glucose tolerance curve, indicating that the peripheral tissues extract a greater portion of glucose from the blood flowing through them than does the liver. In the absence of measurements of peripheral

blood flow, however, it is impossible to determine whether a greater absolute quantity is removed.

As the glucose tolerance curve falls, the arterial level often falls below the peripheral venous level, thus showing that glucose is being contributed to the circulation by the peripheral tissues. This phenomenon probably arises from the back-diffusion of glucose from intercellular fluid as the blood level falls below that in the tissue spaces. The possibility must also be considered that part of the glucose may be contributed by skin, bone and other connective tissues which, unlike muscle, contain phosphatase.

Blood inorganic phosphate was also determined during the glucose tolerance tests. After the injection of glucose there was a reduction of the phosphate level of the blood drawn from arterial, hepatic and peripheral venous sources. This reduction could not be related quantitatively to the glucose level or to the rate of change of the glucose levels.

By application of the liver blood flow technic described by Bradley et al. (*J. Clin. Investigation*, 24: 890, 1945), one can estimate the actual amount of glycogen deposited or broken down in the liver.

The possible application of the technic to the elucidation of problems of the rôle of the liver in amino acid and fat metabolism are discussed.

20. ESTIMATION OF THE HEPATIC BLOOD FLOW AND SPLANCHNIC OXYGEN CONSUMPTION IN HEART FAILURE

J. D. MYERS, M.D. and J. B. HICKAM, M.D.
(introduced by Eugene A. Stead, Jr., M.D.)

From the Duke University School of Medicine, Durham,
N. C.

(This work was supported by grants from the Life
Insurance Medical Research Fund and the Anna
H. Hanes Fund.)

The hepatic blood flow has been measured in a group of patients with cardiac decompensation using the bromsulphalein technic of Bradley et al. The hepatic arteriovenous oxygen differences and cardiac outputs by the direct Fick method were determined in the same patients.

The hepatic blood flows in cardiac failure have been found between 200 and 700 ml. per minute per square meter (normal range, 600 to 1200 ml.). The degree of reduction in flow is in proportion to the reduction in cardiac output,

the hepatic blood flow remaining a quite constant, and normal, percentage of the cardiac output (17 to 27 per cent). Reduction in hepatic blood flow could not be correlated with the level of right arterial or peripheral venous pressure.

Femoral arterial-hepatic venous oxygen differences in the group with cardiac failure ranged from 5.5 to 12.8 volumes per cent. In only one instance was the oxygen difference below 8 volumes per cent.

These values are to be contrasted with the normal range which is 4.0 to 5.8 volumes per cent. By multiplying the hepatic blood flow by the hepatic arteriovenous oxygen difference, the "splanchnic" oxygen consumption is estimated. In normal individuals this ranges from 26 to 56 ml. per minute per square meter. In the patients with cardiac decompensation the splanchnic oxygen consumptions varied from 26 to 50 ml. and represented the normal percentage (av. 26) of the total oxygen consumption.

21. MAXIMUM HEPATIC CLEARANCE OF BROMSULPHALEIN (= Lm, BROMSULPHALEIN) BY NORMAL PATIENTS AND BY CERTAIN PATIENTS WITH HEPATIC DISEASE

G. R. HAWLEY, M.D. (*by invitation*), ALICE SMITH, M.D. (*by invitation*) and M. F. MASON, M.D.

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Tex.

The technic previously described for determination of the maximum hepatic clearance of bromsulphalein (= Lm, bromsulphalein) by dogs (*Am. J. Physiol.* In press.) has been applied to human subjects. Lm (bromsulphalein) in a series of seven normal male subjects of various ages ranged from 13.6 to 16.4 mg./min./sq.M. surface area. Somewhat lower values (9.4 to 13.0, six subjects; 16.0 and 16.9, two subjects) were observed in a series of eight apparently normal subjects who, nevertheless, had a history of a previous illness accompanied by jaundice.

Some values for Lm in patients with frank hepatic disease are as follows: infectious hepatitis and homologous serum jaundice with bilirubinemia, 6.3 to 10.8; two weeks to two months postbilirubinemic phase, 10.8 to 14.3; elemental phosphorus poisoning, acute phase, 6.7; twenty-nine days later, asymptomatic, 10.0; Laennec cirrhosis (three subjects) 3.3 to 6.1; Laennec

cirrhosis (with hepatoma) 6.4; extrahepatic carcinoma with liver metastases, (three subjects) 8.5 to 11.0; Cruveilhier-Baumgartner syndrome (clinical diagnosis) 10.9; carcinoma of head of pancreas with complete obstruction of long duration, 5.4.

22. EFFECT OF ARTIFICIAL FEVER ON LIVER FUNCTION

MYERS HICKS, M.D. and BYRD S. LEAVELL, M.D.
(*introduced by J. Edwin Wood, Jr., M.D.*)

From the Department of Internal Medicine, University of Virginia Hospital, Charlottesville, Va.

The study was designed to determine the effect of artificially induced fever on liver function. Only subjects without evidence of liver disease were selected. The following tests were employed: bromsulphalein, cephalin-cholesterol, prothrombin time, icterus index, van den Bergh and plasma protein. Other observations included determination of temperature, pulse, blood pressure, skin temperature, hematocrit, hemoglobin, erythrocytes and leukocytes. Observations were made prior to induction of fever, during fever and within twenty-four hours after defervescence.

In ten patients twenty-two episodes of fever were induced by intravenous typhoid vaccine. Only the bromsulphalein test showed significant variation. In every instance when fever was present there was an increase in bromsulphalein retention. Values ranged from 4 per cent to 52 per cent above the control figure.

Three patients received pyrogenic doses of typhoid vaccine plus amidopyrine that prevented fever. Bromsulphalein retention was not observed.

In two patients three bouts of fever were induced by external heat. Bromsulphalein retention ranging from 4 per cent to 28 per cent occurred in each instance.

In ten afebrile subjects the bromsulphalein test was repeated using the same interval employed in the experiments outlined above. No increase in bromsulphalein retention was observed with this control procedure.

It is concluded that hyperpyrexia can be responsible for abnormal bromsulphalein retention in the blood. Further study is necessary to determine if the retention is due to hepatic dysfunction.

(Read by Title)

23. ELECTROPHORETIC PATTERN IN MYOCARDIAL INFARCTION

PRESTON LOWRANCE, M.D. (*introduced by Alfred Chanutin, M.D.*)

From the Department of Biochemistry, University of Virginia, Charlottesville, Va.

The plasma proteins of two patients with myocardial infarction have been studied at frequent intervals by means of electrophoresis. The abnormalities observed consisted of a slight depression of the albumin and an elevation of the alpha-1 and alpha-2 globulins and fibrinogen. The distribution of the protein components returned approximately to normal in one patient seven weeks after the infarct occurred. In the second patient, the alpha-2 globulin is still elevated four months after the infarction. There appears to be no direct correlation between the electrophoretic patterns and the changes in the sedimentation rate and the electrocardiogram. Patients with inactive rheumatic valvular disease served as controls and their protein distributions were within normal limits.

It has been shown by many investigators that any condition associated with tissue necrosis is accompanied by a decrease in albumin and an increase in alpha globulin fractions. These characteristic changes were observed in myocardial infarction and may therefore serve as an indicator of the state of the necrotic process in the infarcted myocardium.

24. PHARMACOLOGIC STUDIES ON MYANESIN

ARTHUR P. RICHARDSON, M.D., JAMES L. MORRISON, M.D. and HARRY A. WALKER, M.D. (*introduced by Arthur J. Merrill, M.D.*)

From the Department of Pharmacology, Emory University School of Medicine, Atlanta, Ga.

Interest in alpha ethers of glycerine has been revived by the work of Bradley and Dewey in England, who have claimed that such compounds may be substituted for curare in connection with general anesthesia. We have found that myanesin, the most active of this series, possesses almost no curare-like action but rather it appears to be a very short acting basal anesthetic. By means of two chemical methods for determination of this compound in body fluids and tissues, it has been found that the

compound disappears rapidly from the plasma and there is close correlation between plasma concentration and depressant action. It is distributed widely and occurs in high concentration in almost all tissues and body fluids. Highest concentration after continuous infusion are found in the brain and pancreas. It is apparently rapidly destroyed since less than 1 per cent can be recovered from bile and urine. The ultimate fate of the remainder has not been determined. The most important toxic reactions are: (1) sudden fall of blood pressure on rapid intravenous injection, probably due to direct myocardial depression and (2) local irritation which may result in thrombosis of vessels. Both cardiac depression and local tissue reaction are much less when dilute solutions are employed.

25. COMPARISON IN MAN OF SERUM LEVELS OF CARONAMIDE AND PENICILLIN FOLLOWING MULTIPLE DOSES OF THE DRUGS

MANSON MEADS, M.D., ROLAND LONG, M.D., SHERMAN PAGE, M.D. (*by invitation*) and GEORGE HARRELL, M.D.

From the Department of Medicine, Bowman Gray School of Medicine, Winston-Salem, N. C.

Seventeen ambulatory patients under sixty years of age without cardiac liver or kidney damage received 100,000 units of crystalline penicillin G intramuscularly every four hours for seven days. On the second, third and fourth days, carnomide simultaneously was administered orally to seven patients (Group A) in doses of 2 Gm. every four hours and to ten patients (Group B and C) in doses of 4 Gm. every four hours. One to three levels were determined daily. The samples of serum in Groups A and B were drawn four hours after the preceding dose and in Group C two hours after the preceding dose. The range of individual variation in caronamide and penicillin levels was great. When plotted, the mean value shows little effect of caronamide on penicillin levels in Group A. In Groups B and C the caronamide concentration increased steadily to the fourth day; the penicillin level reached a peak on the third day and remained there through the fourth day. The accumulation of caronamide in concentrations exceeding 20 mg. per cent in the serum is accompanied by a significant rise in serum penicillin level. Short interval or single dose studies have not disclosed this cumulative

effect. Mild toxic reactions were observed with caronamide levels exceeding 40 mg. per cent.

26. DYSFUNCTION OF THE ADRENAL CORTEX IN CANCER PATIENTS

EDWARD C. REIFENSTEIN, JR., M.D., F. HOM-
BURGER, M.D. and KONRAD DOBRINER, M.D.
(introduced by Albert Segaloff, M.D.)

From the Departments of Clinical Investigation and Steroid Chemistry, the Sloan-Kettering Institute for Cancer Research, the Memorial Cancer Center, New York, N. Y.

Evidence will be presented which suggests that patients with cancer have dysfunction of the adrenal cortex. This evidence includes: (1) the nature of certain urinary steroid metabolites; (2) a comparison of the urinary steroid metabolites of cancer patients with those of patients with known disorders of the adrenal cortex; (3) a comparison of the "alarm reaction" following operation in patients with and without cancer; (4) the effect of adrenal cortical extract on the low liver glycogen content of patients with gastric cancer; (5) a comparison of electrolyte defects of patients with gastric cancer with those of patients with Addison's Disease and (6) a comparison of the adrenal cortical response to anterior pituitary adrenocorticotrophic hormone of patients with gastric cancer with those of patients with non-neoplastic non-adrenal diseases. The significance of these results will be discussed.

27. DAILY VARIABILITY OF THE FLUID RESTRICTION AND PITRESSIN CONCENTRATION TESTS FOR RENAL FUNCTION

J. MAXWELL LITTLE, M.D. and GEORGE A. ANDERSON, M.D. (introduced by Harold D. Green, M.D.)

From the Department of Physiology and Pharmacology and Department of Internal Medicine, Bowman Gray School of Medicine, Winston-Salem, N. C.

Interpretation and comparison of the twelve hour fluid restriction and pitressin (10 units subcutaneously) concentration tests for renal function assumes that the daily variability in each is insignificant. This was tested in a random group of students, twenty-five (average six tests) with fluid restrictions and ten (average five tests) with pitressin.

The average σ for the former was 2.9 and for the latter 3.8 units. There was no correlation

between the individual mean values of specific gravity and σ .

Interpreting specific gravities below 1.020 as impaired renal function, the results on the first fluid restriction and pitressin tests compared with subsequent tests were, respectively consistently good function 12, 2; consistently impaired function 2, 1; varying between good and impaired function 9, 4; between impaired and good 2, 3 patients.

Interpreting specific gravities of 1.027 or greater as good, 1.014 to 1.027 doubtful, and below 1.014 impaired function, the respective results were: consistently good function 4, 0; consistently doubtful 10, 5; consistently impaired 0, 0; varying from doubtful to good 8, 3; poor to doubtful 2, 2; poor to good 1, 0. The pitressin test is more variable than the fluid restriction test. Because of daily variability, a single test of either type is of little value if the result indicates impaired or doubtful function.

28. EFFECT OF THE ADRENAL CORTEX ON DIABETES DURING INFECTIONS

LOUIS TOBIAN, JR., M.D. and JACK EDWARDS, M.D.
(introduced by Morton F. Mason, M.D.)

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Texas

The hypersecretion of the adrenal cortex caused by infections and the inhibition by adrenal cortical extracts of the hexokinase reaction of the diabetic muscle suggested that infections produced an exacerbation of diabetes by causing increased adrenal cortical secretion.

To study this, we divided a number of mice made diabetic with alloxan into two groups. One group had intact adrenals; the other group was adrenalectomized and then continuously given .05 cc. of Upjohn's lipo-adrenal cortex every eleven hours.

Both groups received three injections of typhoid vaccine, one every eight hours, and fasting blood sugars were obtained before and after the course of typhoid injections.

The adrenalectomized animals receiving adrenal cortex hormone showed as great a rise in blood sugar level after the typhoid vaccine as the animals with intact adrenals.

Hence, an increased secretion of adrenal cortex hormone after typhoid is not responsible for the exacerbation of the diabetes.

29. DILUTION ACIDOSIS

GEORGE T. SHIRES, M.D. and JAMES HOLMAN, M.D.
(introduced by Morton F. Mason, M.D.)

From the Department of Pathological Chemistry,
Southwestern Medical College, Dallas, Tex.

In studying the effects of the rapid saline administration upon circulation and respiration in the dog, a constant and progressive acidosis of arterial blood has been noticed. Apparently this phenomenon, although previously observed, has received no attention in recent literature. It was also demonstrated that this effect could be prevented by the simultaneous administration of bicarbonate in saline which was balanced to isotonicity.

The acidosis is interpreted as being the result of dilution of the total bicarbonate of the blood by pure saline. Since the CO_2 production of the body tissues remains relatively constant the H_2CO_3 numerator of the blood buffer $\text{H}_2\text{CO}_3\text{-NaHCO}_3$ remains relatively constant and with saline administration it is actually the NaHCO_3 which is diluted, altering pH toward acidity.

This concept should be kept in mind when saline administration is carried out, particularly in the face of existing acidosis or renal damage.

30. PHOSPHATE FRACTIONS IN THE HEART IN
RELATION TO EXPERIMENTAL HEART
FAILURE

GUS G. CASTEN, M.D. (introduced by Morton F.
Mason, M.D.)

From the Department of Pathological Chemistry,
Southwestern Medical College, Dallas, Tex.

The important rôle played by the acid-soluble compounds of phosphorus in the chemistry of muscular contraction has prompted the following study of quantitative changes in these compounds in acute experimental heart failure.

The hearts of rats in which acute heart failure has been produced by a combination of hypervolemia and hyperthermia and by the use of the heart-lung preparation show well marked quantitative decreases in the adenosine triphosphate content.

Comparable animals, subjected to the same experimental procedures but in which cardiac fatigue is not produced, show no changes in the acid-soluble phosphorus compounds, including adenosine triphosphate and creatine phosphate.

31. EFFECT OF INJECTION OF GLUCOSE INTO
THE CEREBROSPINAL FLUID

ROBERT W. LACKEY, M.D. (introduced by Arthur
Grollman, M.D.)

From the Southwestern Medical College, Dallas, Texas

It has recently been reported that injection of glucose into the cisterna magna in the dog and in man elicits changes in blood sugar level simulating those resulting from the intravenous administration of insulin. Since such a reaction would have important implications relative to regulation of carbohydrate metabolism, an attempt at corroboration has been made.

Each of six normal, fasted unanesthetized dogs were given by cisternal puncture 2 ml. of a 5 per cent solution of glucose following the withdrawal of an equal volume of cerebrospinal fluid. Blood sugar determinations were made before and at five, fifteen, thirty, sixty and 120 minutes following the injection. In no instance was a fall in blood sugar observed. Instead, the blood sugar level tended to rise slightly, the increase being more pronounced during the second hour.

The experiment was repeated with three dogs anesthetized with sodium pentobarbital with similar results.

32. USE OF THE ARTIFICIAL KIDNEY

E. E. MUIRHEAD, M.D. and JOHN C. VANATTA,
M.D. (introduced by Arthur Grollman, M.D.)

From the Southwestern Medical College, Dallas, Tex.

The application of the artificial kidney described by Kolff to nine nephrectomized and five normal dogs for one to three hours of dialysis resulted in death of the animals within a maximum period of forty-two hours, usually in less than twelve hours. These results indicate the technical difficulties in the procedure as described in the literature. The procedure, therefore, is not suitable for clinical application in its present status of development.

33. ANTIDIURETIC ACTION OF THE URINE IN
CLINICAL HYPERTENSION

MICHAEL ELLIS, M.D. (introduced by Arthur
Grollman, M.D.)

From the Southwestern Medical College, Dallas, Texas.

In ten of thirteen patients with essential hypertension an antidiuretic substance has been

found in twenty-four hour urine samples. Studies have been made as to its nature, especially in respect to the posterior pituitary hormone, pituitrin.

34. SEROLOGIC STUDIES ON Q FEVER IN THE UNITED STATES

ELIAS STRAUSS, M.D. (*by invitation*), S. EDWARD SULKIN, M.D. and (*by invitation*) ELIZABETH L. WATSON, M.D.

From the Departments of Bacteriology and Medicine, Southwestern Medical College, Dallas, Tex.

The present studies were undertaken to determine whether or not unrecognized Q fever is present in this country and, if so, to estimate its prevalence in different geographic areas and occupational groups. Complement-fixation tests were performed for the detection of serum antibodies against a yolk-sac antigen of *R. burneti* (Nine Mile strain).

The persistence of serum antibodies following natural infection was investigated. Serum specimens were obtained at intervals from individuals who were ill with naturally acquired Q fever in March, 1946. In most instances detectable antibodies, in high titer, were present eighteen months after infection.

Serum specimens were obtained from 1,400 employees of meat packing plants in a Southwestern city. Detectable complement-fixing antibodies were present in 8 per cent and significantly high titers were present in 2 per cent of these individuals. Another group of 1,000 serum samples was obtained from a Wassermann laboratory in the same geographic area. Of this number, 10 per cent had detectable serum antibodies and 1 per cent had significantly elevated titers. In a third group of 500 serum specimens obtained from a Wassermann laboratory in an Eastern city, only 1 per cent had detectable antibodies and none had significantly elevated titers.

These studies are continuing. The question of the specificity of low titers of antibodies has not been settled but it is clear that clinically unrecognized or inapparent infections with Q fever occur in this country. Preliminary observations suggest that occupation and possibly also geographic area may be factors in determining the prevalence of Q fever in the United States.

35. HYALURONIDASE AND HYALURONIC ACID OF GROUP A STREPTOCOCCI

ROBERT M. PIKE, M.D. (*introduced by S. Edward Sulkin, M.D.*)

From the Department of Bacteriology and Immunology, Southwestern Medical College, Dallas, Tex.

Hyaluronidase activity of noncapsulated group A streptococci was detected by growing cultures in broth containing hyaluronic acid and testing the culture supernatant fluid for the mucoid polysaccharide. Of 110 strains, 55 per cent significantly reduced the hyaluronic acid content of the medium in twenty-four hours. When the period of incubation was prolonged to several days, additional strains were found to be hyaluronidase producers. Hyaluronidase could be detected in the culture fluid within the first few hours of growth, reached a maximum concentration near the end of the phase of most rapid growth and exhibited marked instability under various conditions.

Some strains of capsulated group A streptococci also destroyed, in one to seven days, hyaluronic acid present in the medium. This effect was evident not only on added hyaluronic acid but also on the mucoid polysaccharide produced in the culture. These strains, therefore, both produce and destroy hyaluronic acid but the hyaluronidase activity is weak in comparison with many non-capsulated strains.

No quantitative relationship was demonstrated between the amount of mucoid polysaccharide produced and virulence for mice. Neither did virulence of capsulated strains appear to be associated with the rate of disappearance of hyaluronic acid from the cultures.

36. STUDIES ON THE PATHOGENESIS OF RHEUMATIC FEVER

GLADYS J. FASHENA, M.D., ROBERT M. PIKE, M.D. (*by invitation*) and S. EDWARD SULKIN, M.D.

From the Departments of Pathology, Pediatrics and Bacteriology, Southwestern Medical College, Dallas, Tex.

Antirabbit heart sera have been prepared by the injection of rat-heart emulsions into rabbits, with and without the use of the Freund adjuvant. Antibodies to rat-heart and to rat serum were demonstrated by the precipitin test and the collodion particle agglutination technic. Serum antibodies were absorbed from some of

the immune sera by *in vitro* and *in vivo* methods. Young rats were given a series of injections of the immune sera. Control animals received similar injections of (1) normal saline; (2) normal rabbit serum and (3) diluted egg albumin. The animals were sacrificed after varying intervals and the hearts examined histologically. Rheumatic-like lesions consisting of (1) edema and cellular proliferation in heart valves; (2) focal cellular accumulations in the valve ring and (3) focal degenerative changes in the ground substance of the valve ring connective tissue, surrounded by a few mononuclear cells, were detected in many of the animals receiving protein-containing injections but not in the saline-treated controls. These lesions appear to represent a response to foreign protein rather than to specific anti-organ antibodies.

37. COMPARATIVE EFFECTS OF HYPERTONIC SOLUTIONS OF VARIOUS INORGANIC AND ORGANIC SODIUM SALTS, GLUCOSE AND PLASMA PROTEIN UPON THE VOLUME OF THE BRAIN OF ANESTHETIZED DOGS

F. W. KLINGE, M.D., M. LEVEN, M.D. (*by invitation*) and CARL A. MOYER, M.D.

From the Department of Surgery, Southwestern Medical College, Dallas, Texas.

Changes in brain volume attending the intravenous injection of the above hypertonic solutions were observed continuously for periods of eight to eighteen hours. A water-manometer attached to a closed elastic system which was held in place over both cerebral hemispheres by an air-tight artificial lead skull plate was used as the recording system.

The concentration of sodium in all the solutions of sodium salts employed was 1,185 mEq.

per liter of water. These solutions were injected intravenously at a rate that was sufficiently slow to obviate the transitory depression of arterial blood pressure that follows the rapid injections of hypertonic solutions. A dose of 4.03 ml. per Kg. of body weight was uniformly employed.

It was found that sodium succinate produced a greater and more prolonged reduction in brain volume than did sodium lactate; racemic sodium lactate was more effective than sodium chloride and sodium chloride was usually more effective than a mixture of sodium chloride and bicarbonate. No secondary increases of the brain volume above the control level were seen following the injection of the above salts.

A 25 per cent solution of salt-poor human albumin given in doses of 6 Gm. of albumin per Kg. of body weight had no effect upon the volume of the brain during the injection period; during the postinjection period the volume of the brain usually increased.

Transient, small reductions of intracranial volume followed the injection of a 25 per cent solution of glucose in water (dosage of 4 to 6 cm. per Kg.). An increase in intracranial volume above the initial levels usually followed the initial reduction.

No correlation could be found between the effects upon the volume of the brain of the above mentioned substances and the simultaneous changes in the blood pressure, the body temperature, the load of water or the rate of urine flow.

The differences between the actions of the various sodium salts cannot be attributed to variations in effective osmolar concentration of the solution employed; it seems probable that the characteristics of the anion may be responsible for them.

Book Reviews

The Principle and Practice of Medicine. By Henry A. Christian, M.D. 16th Edition. Pp. 1539. New York, 1947. D. Appleton-Century. Price \$10.00.

In these days of specialization and laboratory evaluation, when medical practice leans toward a highly scientific appraisal of physiologic and anatomic disturbances now increasingly subject to more exact diagnosis and when therapy is rational and subjected to the law of controls, the medical student or practitioner of medicine not infrequently finds himself beset on the one hand by the cries of the expert urging him into more and more detailed and expensive workups for his patients and, on the other hand, by the five-minute history, physical and prescription writing type of consultation (so frequently dictated by the necessities of time and economics) but happily now belonging to a disappearing medical era. In this quandary it is refreshing to have recourse to a medical textbook cognizant of each extreme and presenting in a readable fashion a mature synthesis based on the wise judgment of such a seasoned and competent teacher as Dr. Henry A. Christian.

"The Principles and Practice of Medicine" first appeared in 1892 under the hand of Sir William Osler and has been edited since 1938 by Dr. Henry A. Christian. The present 16th edition continues the fine tradition of its noteworthy past.

The subject material is subdivided with an etiologic breakdown when possible; when not, into systemic diseases. No significant omissions were noted by this reviewer. Each topic is further separated by special head-

ings for etiology, pathology, symptoms, diagnosis and treatment. An adequate list of pertinent and up-to-date references is consistently presented. The typography is satisfactory although those who appreciate illustrations will find none. An excellent 156 page index, a table of normal laboratory values and a history of medicine from 1892 to 1947 add to the usefulness of the volume.

This, then, is a medical textbook in keeping with its distinguished tradition.

F. K. H.

Diseases of the Nose and Throat. By Charles J. Imperatori, M.D. 3rd Edition. Pp. 576, with 480 illustrations. Philadelphia, 1947. J. B. Lippincott Company. Price \$12.00.

This is the third edition of a well known text book. Diseases of the nose and throat are presented in a clear, concise and practical manner. Office procedure and treatment are discussed in detail. This is followed by a complete description of the pathology. There are 480 excellent illustrations, many of which show the microscopic anatomy of the disease under discussion. Treatment has been brought up to date by revision of chapters to include the newer advances of chemotherapy and radiotherapy. Dr. Ira I. Kaplan has written the chapter on Radium and Roentgen Ray. Dr. Andrew A. Eggston has written the chapter on Laboratory Aids. The experience of the authors make this an authoritative work. It can be recommended as a textbook for students and as a reference work for the practicing physician.

D. C. B.

Editorial

Cancer Research

CANCER is an inclusive expression which we use to cover many different diseases which have a common characteristic, namely, abnormal and invasive growth. Descriptive knowledge of cancer is elaborate, and we have practical means for alleviation and sometimes for cure in surgical extirpation and in radiation therapy. The pathologist, the surgeon and the radiologist are the clinical team which has been most concerned with diagnosis and treatment of the disease. More and more we can expect new developments, both in terms of diagnosis and treatment, to expand the groups having a very definite place in the total care of the cancer patient. All physicians, general practitioner and specialist alike, must concern themselves with this problem. The internist must become one of the key figures in interdisciplinary clinical and research efforts.

Research in experimental cancer is pointing to many complex host factors as a background in the development of tumors. Among these are endocrine dyscrasias and altered metabolism, which are linked to cancer in varying degrees and combinations. Present knowledge warrants the assumption that superimposed on local causative agents are complicated systemic alterations. We do not fully understand the significance of the mammary tumor agent, a probable virus, in breast cancer of certain strains of mice, nor of the implication of viruses in human breast or other cancers.

There is thus a great need for participation in cancer control by more specialists than the three groups named. It is everyone's problem, not that of a few.

Early care of the patient by present means can save tens of thousands more lives each year than are now saved. But our final hope lies in research. Research in cancer has interested many workers in the fundamental sciences, and an ever widening search for basic information on cell growth and differentiation has been launched. Fundamental studies in the field of growth are worthy of extension on a much larger scale. More and more research directly on the problem of human cancer must be encouraged and increased. More studies should be made in man of enzyme systems, proteins, lipids and steroids, and of metabolism generally, including greater application of both stable and radioactive isotopes as tracers and as therapeutic agents alone and in combination with other materials. The search for cancer tests and cancer chemotherapeutic agents is so important that great expansion in scope is indicated.

The history of medicine points time and time again to the discovery of satisfactory methods of treatment or of cures in advance of the finding of answers to all fundamental and background aspects of various problems. It is foolhardy to predict that major answers in cancer research will come in such fashion, yet the possibility cannot be overlooked and we are warranted in pressing the more empirical research approach.

to the problem as long as we do not let up on our fundamental studies.

What do we need in addition to that which we now have? We need the interest of more physician-investigators, and of other scientists skilled in all of the specialized fields of the medical and biologic sciences. We need more teachers of scientists and economic security for these teachers. We need to follow present leads and we need new research ideas. These will come as the scientist potential grows with the addition of "new blood." We need more teamwork and interdisciplinary effort. We need more laboratories and especially do we need more research beds with associated laboratories. We need more adequate, assured long range financing of men and of equipment, supplies and facilities (including research beds) by endowment and other philanthropy, by support by foundations and other voluntary agencies, and by government at all levels. Hektoen* once wrote "research in competent hands should not be restricted for want of anything which money can provide." The "competent hands" exist. The public, through the American Cancer Society and other voluntary agencies, and the Congress of the United States, have given liberal support to finance cancer research throughout the United States during the present year. Federal funds in the amount of \$5,000,000 are available through the National Advisory Cancer Council of the National Cancer Institute, one-half to finance individual cancer research projects and one-half for laboratory and clinical research facility construction in non-Federal

research centers. The Atomic Energy Commission has \$5,000,000 earmarked by Congress for activities in the cancer field, part of which will be used for research grants. In addition there are extensive research fellowship programs in the National Cancer Institute and the Atomic Energy Commission. Large sums are available from the Committee on Growth of the National Research Council, acting for the American Cancer Society, and from other foundations and organizations to support research projects and research fellowships. In addition the American Cancer Society has embarked on a praiseworthy program of giving sizable "institutional" research grants. However, in spite of these programs there is not enough money available at the present time to support many worthy research projects. We are warranted in providing larger sums for cancer research than are now available, not only for the results which will come in solution of the cancer problem but also for the results which will be of value in better understanding of fundamental biology and of many diseases in addition to cancer.

The American public has indicated clearly its interest in greater research efforts in cancer. Physicians and other related professional groups must take up the challenge and drive intensively and relentlessly for greater and speedier progress in cancer research and control. Teamwork on the part of all professional and lay groups can go far to make the solution of the cancer problem a reality.

LEONARD A. SCHEELE, M.D.†

Surgeon General

United States Public Health Service

† Formerly Director, National Cancer Institute.

* HEKTOEN, LUDVIG. Progress Against Cancer. Pamphlet of American Medical Association, 1946.

Pneumonia and Erythema Multiforme Exudativum

Report of Four Cases and Three Autopsies

MAXWELL FINLAND, M.D., LESLIE S. JOLLIFFE, M.D.
and FREDERIC PARKER, JR., M.D.

Boston, Massachusetts

THE vesicular or bullous type of erythema multiforme with severe systemic symptoms and involvement of the conjunctivae and the mucous membranes of the orificial surfaces has been considered to be rather rare.¹⁻⁴ Renewed interest in this condition, however, has recently brought forth a number of reports of such cases, occurring singly or in small groups, with lesions of varying extent and severity and considered under a variety of designations. In one hospital for contagious diseases thirty-three patients were seen over a period of thirteen years;^{5,6} seventeen were encountered in Canadian military hospitals in a few months;⁷ six cases which occurred over a period of three years were reported from Fort Bragg;⁸ a series of twenty subjects with various combinations of lesions and observed over several years were reported from another military installation;⁴ ten cases were studied in one large naval hospital⁹ and two patients were admitted to a civilian general hospital only eighteen days apart.¹⁰

The milder forms of erythema multiforme exudativum and those with relatively few lesions are rather benign, but even with the more severe forms most of the patients recover with varying rapidity and without sequelae save for occasional instances of

permanent and disabling damage to ocular structures.^{3,4,6,11,12} Soll⁴ stated that no deaths have been reported in English literature except for one questionable instance; Lever³ collected only four fatal cases from the literature prior to 1944 but a larger number have since been reported. Thus there were five deaths among twenty-eight patients at the Willard Parker Hospital⁵ and two deaths among the seventeen cases reported from the Canadian military hospitals.⁷ Another fatal case in an American army hospital is mentioned in the report of the Commission on Acute Respiratory Diseases and at least two additional fatalities in patients with a similar syndrome following the use of sulfadiazine have also been recorded.^{13,14}

The association of pulmonary lesions with erythema multiforme exudativum has recently been reviewed by the Commission on Acute Respiratory Diseases and lesions clinically resembling those of primary atypical pneumonia were reported in three of the six patients whom they observed at Fort Bragg.⁸ Lesions of the respiratory tract including pneumonia were also frequent in the Canadian army cases and prompted the designation "mucosal respiratory syndrome."⁷ Markham¹⁵ described a fatal case of "atypical viral pneumonia" with super-

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Mallory Institute of Pathology, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

imposed severe conjunctivitis, membranous stomatitis, bullous cutaneous eruption and balanitis and stated that four of five similar cases were fatal.

Cases presenting the characteristic picture of primary atypical pneumonia of unknown etiology,^{16,17} particularly those of more than moderate severity, were recognized more frequently at the Boston City Hospital and in the surrounding communities during the fall and winter of 1942 to 1943 than at any other time before or since. The severity of these atypical pneumonias is attested by the occurrence of fifteen deaths in a group of 200 such cases that were studied between September 1942 and January 1944.¹⁸ Early in the course of this outbreak a patient was admitted to the Boston City Hospital with the bullous type erythema multiforme with characteristic physical, x-ray and other findings of primary atypical pneumonia. The patient died and autopsy confirmed the findings in the lungs. Only three weeks later a second patient was admitted to the same medical service with very similar findings. This patient recovered but only after a very stormy course. Three months later a third patient with similar findings was admitted to another medical service; he also had a stormy course and, after a brief remission during which there was some improvement, a secondary bacterial infection of the cutaneous and pulmonary lesions set in and the patient died. Autopsy in this patient revealed evidence of both primary atypical pneumonia and of secondary necrotizing bacterial infection of the lungs.

Numerous other patients with primary atypical pneumonia of unknown etiology, of varying severity and associated with vesicular types of erythema multiforme were seen during this time and in the subsequent months through the courtesy of many physicians in civilian and military hospitals who were aware of our interest in such subjects. The patients that were seen, however, usually had very few lesions of the skin or mucous membranes and their illness was rather mild; none had the combination

of a severe illness with widespread atypical pneumonia and extensive mucocutaneous lesions. Our attention was also called to a number of patients with erythema multiforme exudativum, many of them with ocular involvement, with lesions of the orificial surfaces and some of them acutely ill, but they did not have clinical or roentgenographic evidence of the characteristic and extensive pneumonitis and none of them were fatal.

The three cases cited appeared to be rather unique at the time and of considerable interest because of the association of extensive mucocutaneous and pulmonary manifestations. A fourth patient observed a few months later exhibited a fulminating course of the bullous type of erythema multiforme and autopsy revealed only minimal pulmonary lesions. In the latter case, and in the patient previously mentioned who recovered, there was a history of contact with dead birds. There was also serologic evidence suggestive of infection with a psittacosis-like virus in the patient who recovered and in the first fatal case. These unusual circumstances have prompted this report of the four cases, including the autopsies in the three fatal ones.

CASE REPORTS

CASE 1. A seventeen year old, white messenger boy was admitted to the Boston City Hospital, August 26, 1942, complaining of cough and sore throat. His illness began two weeks prior to entry with a cold, characterized by coryza and malaise, and a week later he developed a cough productive of gray sputum which persisted to entry. On the day before admission he first noted a severe sore throat with dysphagia and the sputum became stained with dark streaks of blood. That evening he had a shaking chill and began to experience some anterior chest pain with cough. He had received no sulfonamide drugs nor any other medication. Both family history and past history were non-contributory.

When first seen the patient was well developed and moderately well nourished, acutely ill and breathing rapidly. There was marked injection of the scleral and palpebral conjunctivae. The

lips were dry and cracked and covered with bloody crusts; on the buccal mucous membranes there were many vesicles from 2 to 8 mm. in diameter, some with clear fluid and others with hemorrhagic material and each surrounded with an area of intense erythema. The pharynx was diffusely red and covered with small patches of gray exudate. There were a number of scattered vesicles on the neck. Some of these had become pustular and others had a typical rosette appearance. There were a few small, firm, non-tender nodes felt in the submaxillary, anterior cervical and left axillary regions. In the lungs there were a few scattered crepitant râles and some inconstant, high-pitched, sibilant râles. There were also some areas of diminished breath sounds but no dullness. The heart sounds were rapid but otherwise normal. The rest of the examination was negative.

The hemoglobin was 86 per cent; red blood count 4,170,000 and white blood count 12,200 with 40 per cent mature polymorphonuclear neutrophils and 35 per cent young forms. The urine was essentially negative except for a few white blood cells and red blood cells in occasional specimens. The blood non-protein nitrogen was 24 mg. per 100 cc. Blood culture was negative and a throat culture yielded predominantly alpha hemolytic streptococci and a few other mouth organisms. Serologic tests for enteric and heterophile agglutinins and the Hinton test were all negative. X-ray of the chest showed some infiltration in the region of the right middle lobe.

The patient was given routine oral doses of sulfathiazole on entry but did not take them well. He was therefore given 5 Gm. of sodium sulfadiazine intravenously in 1,500 cc. of 0.85 per cent saline followed by 2.5 Gm. in 700 cc. of 5 per cent dextrose in saline twice on the next day. Thereafter, he was maintained on 1 Gm. of sulfadiazine by mouth every four hours throughout his stay. After the second day all medications and feedings were given through a Levine tube. He received a high caloric and high vitamin diet with multiple vitamin supplements. Sulfathiazole ointment was applied to open lesions of the skin. Boric washes and ammoniated mercury ointment were used for the ocular lesions. Dilute sodium peroxide and perborate were used for mouth washes. Codeine with elixir of terpin hydrate was given for the cough and some barbiturates for sedation. The patient was

in an oxygen tent throughout the latter part of his stay in the hospital.

After entry numerous vesicles surrounded by areas of erythema appeared in rapid succession on the skin of the neck, upper trunk and upper arms and also on the pharyngeal wall and buccal mucous membranes. Others later appeared on the lower part of the trunk, on the extensor surfaces of all the extremities and also involved the scrotum and urethral meatus. Desquamation of the surface of some of the lesions was present, many of the vesicles became pustular and some became hemorrhagic. Dysphagia increased markedly. The conjunctivae became chemotic, the lids became swollen and vesicles appeared on the lid margins which later became hemorrhagic and encrusted. The number of râles increased in both lungs, more in the dependent areas. There were also patchy areas of dullness and diminished breath sounds which varied in location from time to time. The respirations increased in rate and became more labored; there was increasing cyanosis. There was also considerable sweating. The temperature remained elevated at about 104°F. throughout most of the course except between the fifth and seventh days in the hospital when it ranged between 101 and 102°F. The pulse and respirations also dropped somewhat during this period but during the last two days the temperature, pulse and respirations rose steadily.

The hemoglobin, red and white blood counts all remained essentially the same as at entry. The level of free sulfadiazine in the blood after the intravenous injections was about 10.3 mg. per 100 cc. but dropped gradually to 5.8 on the fifth day and was 28.8 soon after an intravenous dose on the eighth day. A few sulfadiazine crystals were seen in the urine on the fourth day. The blood non-protein nitrogen was 24 mg. per 100 cc. on three occasions but there was a terminal rise to 47. Guaiac tests on the feces were negative on four occasions. An electrocardiogram taken on August 28th showed no abnormalities except for the rapid rate.

Successive sputum cultures showed increasing numbers of hemolytic *Staphylococcus aureus* in addition to *Streptococcus viridans* and other mouth organisms in varying numbers. Numerous blood cultures were negative. The complement fixation test for psittacosis was positive (4+) in 1:256 dilution of serum on August 28th, and on September 3rd the serum was

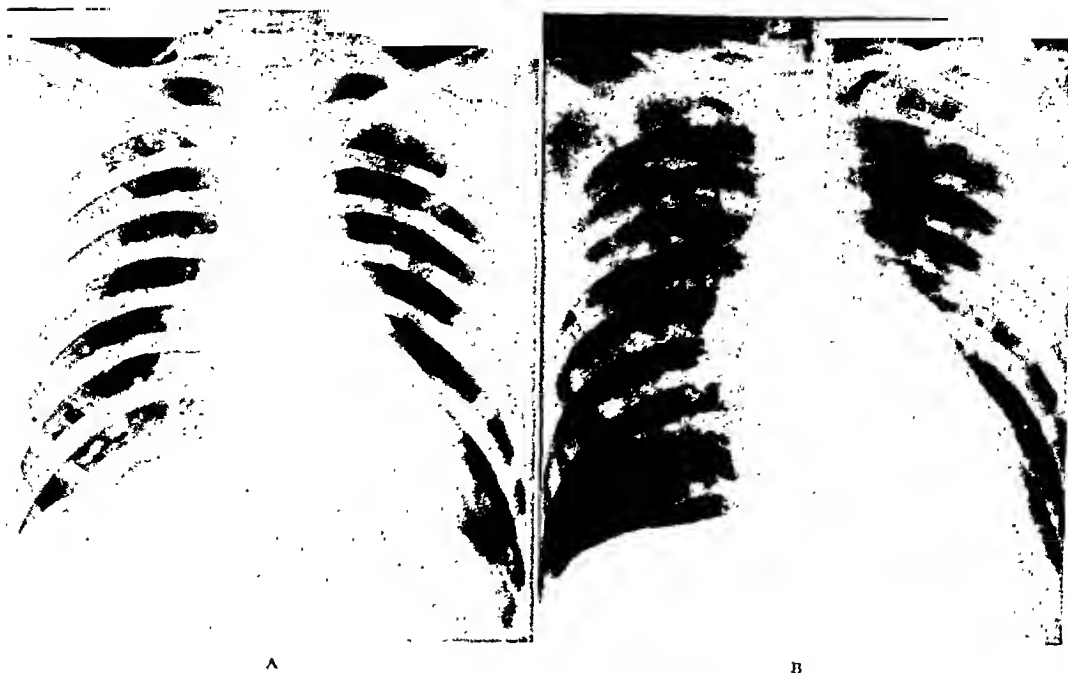


FIG. 1. Case 1. X-rays taken on admission (A) and four days later (B) showing extension of the soft, nodular densities throughout both lung fields.

positive (4+) in 1:256 and 2+ in 1:1024. The latter serum also had a cold agglutinin titer of 1:640. Some of the sputum was fixed and examined histologically and showed chiefly polymorphonuclear leukocytes; no cells with inclusion bodies were seen.

X-ray of the chest on August 31st showed irregular, mottled consolidation of both lower lobes and of the mid-right lung field. Dyspnea and cyanosis increased progressively and breathing became labored after that time. The patient became increasingly disoriented and delirious but there were no abnormal neurologic signs detected and the neck remained supple. He died on September 3rd. A lumbar puncture done shortly before death yielded entirely normal cerebrospinal fluid and the pressure and dynamics were also normal.

The clinical chart, some of the roentgenograms and the skin and ocular lesions in this case are shown in Figures 1 to 3.

Autopsy was performed eighteen hours after death. Over the entire body there were scattered blebs containing clear fluid and varying in diameter from 0.5 to 2.0 cm. There were many dried blebs and many others where the superficial layers were absent, revealing a red-brown, smooth base. Some of the latter were crusted. The eyelids were dark red, ulcerated and encrusted. The conjunctival vessels were congested and there were irregular areas of subconjunctival

hemorrhages. The anterior surface of the scrotum and the distal 3 cm. of the skin over the penis were ulcerated and encrusted. There were palpable axillary and inguinal lymph nodes.

There was a very thin layer of fibrinous exudate over both lobes of the left lung and over the lower lobe of the right lung. In addition a small amount of fibrinous, mucoid exudate was present between the base of the left lung and the diaphragm. The combined weight of the lungs was 1,200 Gm. The middle lobe of the right lung was subepitantal and had a white surface. All of the other lobes were purple-red and showed markedly decreased to absent crepitation. The cut surfaces were dark red-purple and no purulent material could be expressed. There was a miliary nodular appearance, more of the lower lobes, with some dark areas of hemorrhage, congestion and atelectasis, especially of posterior and dependent portions. The mucosa of the bronchi and trachea was congested. The tracheobronchial lymph nodes were not enlarged.

The gastrointestinal tract was normal along its entire length except for slight congestion of the gastric mucosa. The spleen, liver, adrenals, kidneys, ureters and bladder all appeared normal.

The brain weighed 1,760 Gm. The convolutions were slightly flattened. The cerebral veins

were markedly congested. The lateral ventricles and the sulci over the insulae were almost completely obliterated. No gross lesions were seen.

The histologic changes varied greatly in different areas of the lungs. In some the alveoli were essentially normal, in others they contained precipitated albumin and in still others there were fibrin and red blood cells. In many alveoli the lining cells were swollen and vacuolated and a few showed mitotic figures. In such areas the exudate in the alveoli was composed of mononuclear cells, desquamated alveolar lining cells, an occasional multinucleated cell and a rare giant cell of the foreign body type with nuclei up to twenty in number. In addition there were plasma cells in the alveolar exudate. In places the bronchioles contained numerous polymorphonuclear leukocytes and clumps of cocci. There was a marked peribronchial and perivascular infiltration of plasma cells, some lymphocytes, a rare mast cell and eosinophil. In addition there were some large, immature cells of an unidentified type. There was an infiltration in the submucosa of the trachea and about the glands with lymphocytes, many plasma cells and an occasional mast cell.

The spleen was congested and the pulp contained plasma cells in foci and adjacent to the trabeculae. Sections of the liver and kidney showed some plasma cells and lymphocytes in the interstitial tissue. The bladder was congested and its wall infiltrated with lymphocytes, plasma cells, polymorphonuclear leukocytes, eosinophils and mast cells. One acute vascular lesion was noted with fibrin in the wall of the blood vessel. The lymph nodes were infiltrated with immature cells, either lymphoblasts or histioblasts, and some plasma cells and large mononuclears. The testes showed markedly diminished activity, no adult spermatozoa being present. There were few mast cells and lymphocytes in the interstitial tissue. In sections of the bone marrow there were numerous myelocytes, some metamyelocytes and only a few adult polymorphonuclears. The red cells series and the megakaryocytes appeared normal. There were a considerable number of plasma cells present.

There were a few scattered, large mononuclears, lymphocytes and plasma cells in the cerebral meninges. The phrenic nerve showed occasional lymphocytes and plasma cells about the blood vessels in the center of the nerve while the vagus nerve showed no changes. There was a focus of lymphocytes, rare large mononuclears



FIG 2 Case 1. Lesions of the ear, eyelids, lips, neck and upper chest (A), and of the penis and scrotum (B) as they appeared at the time of death

and plasma cells in the posterior lobe of the pituitary adjacent to the pars media.

Sections from the skin showed vesicle formation. The covering epithelium was necrotic. The base of the vesicle consisted in part of intact epithelium and in part of necrotic connective tissue. The content of the vesicle varied. In part it was composed of precipitated albumin and fibrin, in part of polymorphonuclear leukocytes, large mononuclear cells and fibrin and here there were a fair number of diplococci. Some of the hair follicles and coil glands were necrotic.

The necrotic connective tissue was infiltrated with polymorphonuclear leukocytes and large mononuclears. In the deeper portions of the corium there was a perivascular infiltration of large mononuclears, lymphocytes, plasma cells and an occasional eosinophil and mast cell. The

erasing number of staphylococci in the sputum and the purulent character of the exudate found in the lumen of the bronchi.

The pulmonary lesion was characteristic of primary atypical pneumonia clinically and roentgenographically. The pathologic

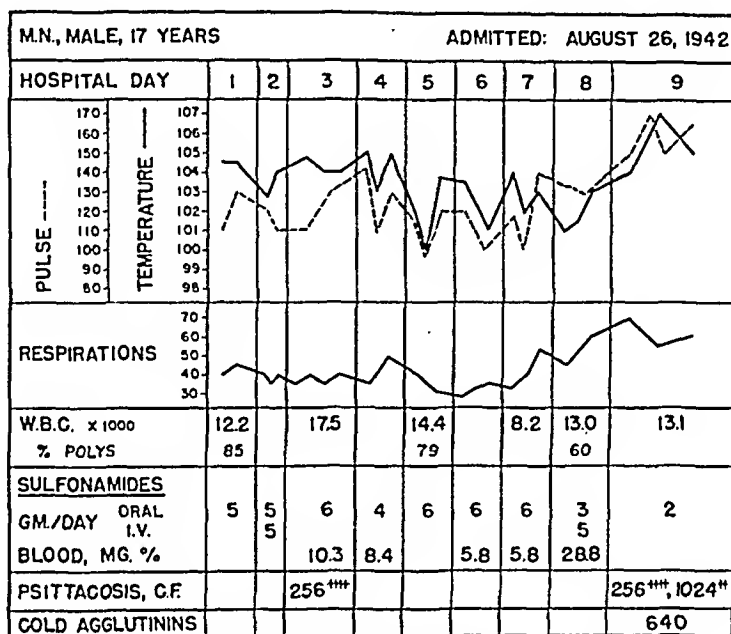


FIG. 3. Clinical chart and some relevant data in Case 1.

blood vessels in the necrotic connective tissue were thrombosed.

Cultures of the heart's blood yielded no growth. Hemolytic Staph. aureus was cultured from the right lower lobe, left lower lobe, pleura and liver, and the latter contained an enterococcus in addition.

Microscopic sections of the skin and lungs are shown in Figures 4A, B and C.

Comment. The illness in this patient began with symptoms of an acute upper respiratory tract infection followed by cough and then substernal pain. The first evidence of mucocutaneous manifestations was the sore throat and dysphagia. The bloody sputum may have been the result of irritation and desquamation of the lesions in the mouth. There was obviously a tracheobronchitis but no evidence of involvement of the trachea and bronchi with lesions similar to those of the skin and mucous membranes was found postmortem. It is also of interest that no ulceration of these structures occurred in spite of the in-

findings were consistent with non-bacterial pneumonia in all sections and the only evidence of bacterial infection was in the bronchioles which contained polymorphonuclear leukocytes and clumps of cocci. The mucosa of the bronchioles, however, was intact and their walls were infiltrated with plasma cells. The skin lesion showed only slight evidence of secondary infection, otherwise the mononuclear type of exudate suggested a reaction to a non-bacterial agent. No elementary or inclusion bodies were found in sections of the lungs or of the skin lesion. The brain showed congestion and a negligible cellular reaction of the meninges but was otherwise normal.

There was no history of drug ingestion prior to the onset of the illness or before admission to the hospital, and no personal or family history of allergy was elicited. Although sulfonamides were administered throughout the hospital stay and the pulmonary and mucocutaneous lesions seemed to get worse during that time, it is not possi-

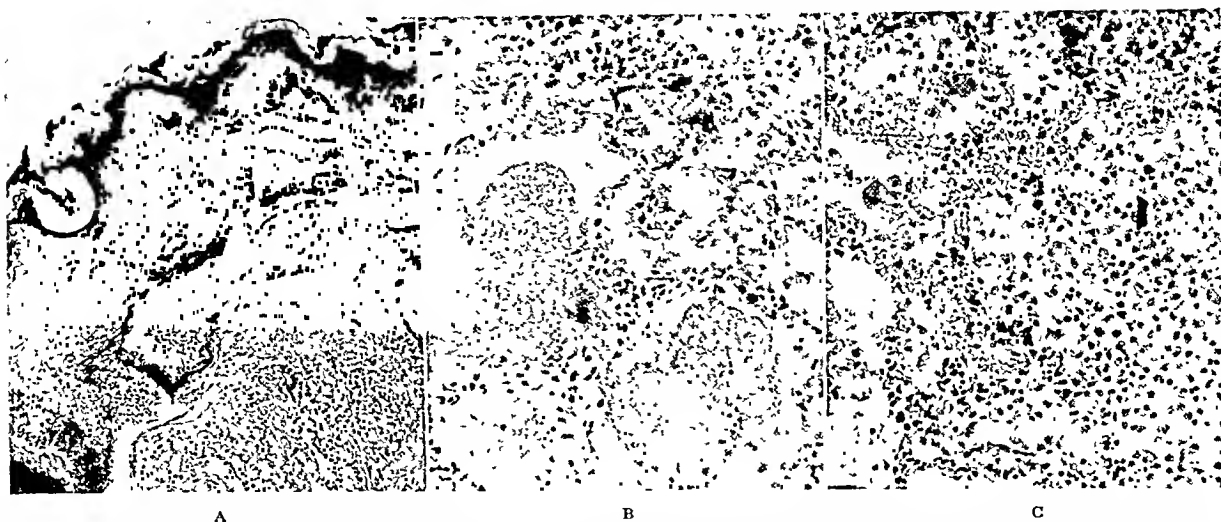


FIG. 4. Case I. A, section through a skin lesion showing vesicle formation with raised epidermis, necrosis of overlying epithelium, exudate of polymorphonuclear leukocytes and fibrin in the necrotic connective tissue and of mononuclear cells in the deeper layers ($\times 70$). B, section from the lung showing alveolar exudate of fibrin and red blood cells ($\times 125$). C, alveolar exudate of mononuclear cells ($\times 150$).

ble in this case to ascribe any of these manifestations to these drugs. On the other hand, the failure of the bacterial infection to advance more than it did either in the lungs or in the skin may be ascribable to the bacteriostatic effect of these drugs.¹² Cases of erythema multiforme bullosum occurring during sulfonamide treatment and ending fatally have been described.^{13,14} One case, with every extensive involvement and a severe febrile course but ending in complete recovery, was observed in this hospital. In that case the cutaneous lesions first appeared on the eighth day of treatment with sulfamerazine for pneumonia and the lungs had already cleared at the time.

As to other etiologic possibilities, the only one suggested by the data available is psittacosis. The complement fixation test done with a psittacosis virus was strongly positive on August 28th and September 3rd but no substantial rise was demonstrated. These dates correspond to the sixteenth and twenty-fourth days respectively after the first symptoms of coryza, and the ninth and sixteenth days after the onset of the cough. No definite history of exposure to birds was elicited. Furthermore, the cold agglutinin titer was very high and corresponded to the titers found in other severe cases of primary atypical pneumonia of

unknown etiology.¹⁸ Cold agglutinin titers of this magnitude have been demonstrated in other cases of atypical pneumonia from which a virus transmissible to chick embryos, cotton rats and hamsters was isolated,¹⁹ but not in proved cases of psittacosis or ornithosis.^{19,20} Attempts to isolate a virus from the sputum, bleb fluid and lungs in this patient were unsuccessful but the methods used were not optimal for that purpose.

CASE II. A twelve-year old girl of Greek descent was admitted to the hospital on September 25, 1942. She had been in good health until six days previously when she developed headache, malaise, nausea and vomiting which continued to the time of admission. Two days later she developed a severe cough and went to bed. On the next day she had two shaking chills after which she developed a sore throat, dysphagia, red and sore eyes, a stuffy nose, substernal pain aggravated by the cough and a fever which rose to 104°F. Two weeks prior to entry she saw a dead pigeon lying on the street, poked it about, then wrapped it up in paper and threw it down the sewer. She had no other known exposure to birds or to persons with rashes or with respiratory infections.

On admission she appeared acutely but not severely ill. Her temperature was 103°F., pulse 120 and respirations 24. The palpebral and scleral conjunctivae were markedly injected, there was a postnasal mucoid discharge, the pharynx was diffusely injected and a few shotty,



FIG. 5. Case II. Appearance of mouth, eyes and lips (A) and of the tongue (B) on admission; edema of lids and face and hemorrhagic crusts on lips three days later (C); erythematous and vesicular lesions of the lateral trunk and forearm one week later (D).

non-tender cervical lymph nodes were felt. The chest was resonant throughout and only a few scattered musical râles were heard. The rest of the physical examination was negative at this time.

On the following day the patient became markedly prostrated, apathetic and lethargic. Scattered patches of dirty, gray exudate appeared on the soft palate, tongue and uvula, the conjunctivitis had become purulent, fine crepitant râles appeared in both lungs and a rash began to appear on the neck, chest and upper extremities. The skin lesions appeared first as fine maculopapules which rapidly assumed erythema iris forms with central vesicles each surrounded by an inner clear zone and an outer zone of deep erythema. Individual lesions at this time resembled those of chickenpox.

The patient was then put on full adult doses of sulfadiazine by mouth and sulfathiazole ointment was used on the eyes. During the ensuing week the temperature was irregular and

ranged between 100° and 105°F., pulse 120 to 150 and respirations 40 to 50. The patient appeared critically ill and was kept in an oxygen tent. The pneumonic process spread to involve all of both lungs with numerous fine and medium crepitant râles but no definite signs of solidification. The ulcerative stomatitis spread to the entire oropharynx which was covered with a pseudodiphtheritic membrane that could be removed with difficulty leaving an underlying bleeding surface. The lips and eyelids became markedly swollen and vesicles appeared at their margins. Vesicular lesions also appeared around the vaginal and anal orifices and became ulcerated. New lesions appeared on the skin over the entire trunk and all of the vesicles became bullous. (Fig. 5.)

Early in the second week the bullous lesions were mostly emptied of their contents leaving hemorrhagic maculopapular lesions and the margins of the lips and eyelids had become encrusted and hemorrhagic. The conjunctivae

had become chemotic and small superficial ulcers developed on the cornea. The pneumonia reached a peak at this time and râles in the lungs then became somewhat fewer. The general condition of the patient improved slightly and the temperature began to drop but then rose again. The sulfadiazine was omitted on October 4th because the possibility of a drug fever was considered but the temperature continued to rise and the patient again became increasingly toxic. She had been given two transfusions during the first week because her hemoglobin was only 10 Gm. per cent and another transfusion at this time produced a severe chill with a rise in temperature to 107°F. Sulfadiazine was given again from October 6th to 10th after which she again improved and the temperature dropped gradually to normal.

The skin began to desquamate during the third week leaving a bright red, scaly surface which left reddish-brown areas of pigmentation after they were healed. The stomatitis had cleared by the end of the third week and the conjunctivitis and keratitis improved steadily and later healed completely without residual. Shotty lymph nodes were felt in the cervical, axillary and inguinal regions and the spleen was felt during the third week. Another bout of fever with daily temperature rises to 101 to 103°F. lasted for two weeks and a third course of sulfadiazine was given for five days during the latter part of this period after which the fever gradually subsided. The lungs cleared progressively until only occasional, fine crepitant râles were heard after the third week.

The blood hemoglobin rose from 10 to 13 Gm. per cent after the transfusions and then again dropped to between 10 and 11.5 Gm. The white blood count was 12,000 on admission with 86 per cent polymorphonuclear neutrophils but dropped to 4,200 on the third day and fluctuated up to 9,250 with 82 to 94 per cent neutrophils. Only occasional eosinophils were seen, not over 1.5 per cent at any time. During sulfadiazine administration the blood concentrations of the free drug ranged between 9 and 14.6 mg. per 100 cc. The blood non-protein nitrogen was normal and the urine examinations were negative except for sulfadiazine crystals and a few leukocytes in the sediment of some specimens. The first x-rays of the chest showed mottled, soft areas of density mostly in the left mid-lung field but subsequent ones on the fifth and eighth hospital days showed nodular



FIG. 6. Case II. X-ray on October 3rd showing nodular densities in both lung fields.

densities throughout both lung fields but these had entirely cleared by the end of the second week. X-ray lesions in the lung are shown in Figure 6.

Smears of the oral and pharyngeal exudate showed a large variety of organisms but repeated cultures yielded predominantly alpha hemolytic streptococci and *Staph. aureus* in varying numbers. Cultures of the blood and of vesicle fluid showed no growth, those of the conjunctival exudate yielded *Bacillus coli* and diphtheroids on some occasions and *Staph. aureus* on others. The results of studies of the serum for psittacosis and Q fever antibodies and for cold agglutinins are shown with the clinical chart in Figure 7.

Comment. The onset in Case II was with rather non-specific manifestations of infection and the first localizing symptoms resulted from the oral and ocular involvement which were followed by appearance of skin and pulmonary lesions. Sulfadiazine was not used until some of these lesions had already appeared and it did not influence their course except insofar as it may have limited the amount of superimposed bacterial infection. The dermatologic picture was characteristic of the more severe type of erythema multiforme exudativum with involvement of the ocular and orificial

surfaces. Clinical and x-ray findings in the lungs were characteristic of the severe and diffuse form of non-bacterial pneumonia with miliary nodular lesions involving most of both lung fields. The recurrent bouts of fever in this patient are not entirely ex-

also a steady and significant rise with subsequent fall in the titer of cold agglutinins. This, too, is of interest in view of the high titer of cold agglutinins later in the disease in Case I.

While no definite evidence was obtained

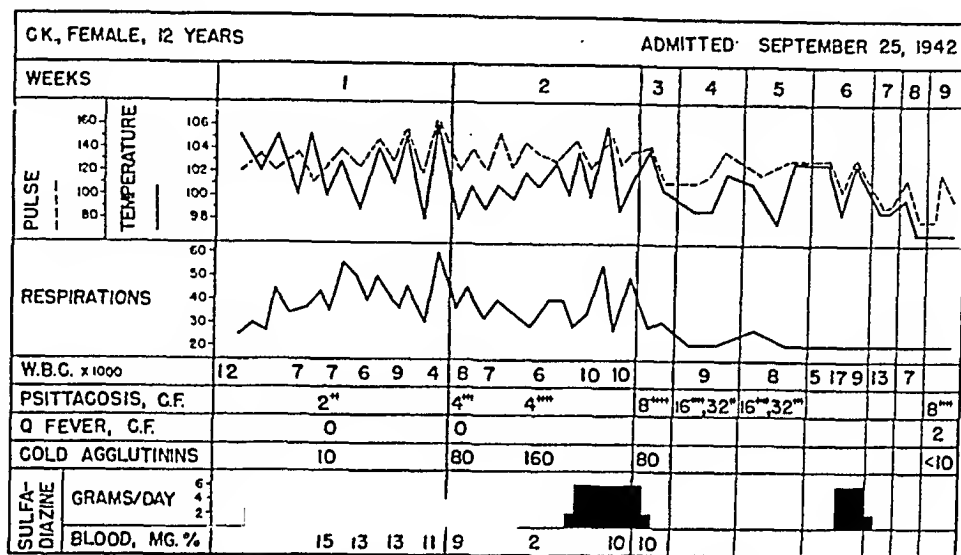


FIG. 7. Clinical chart and certain relevant data in Case II.

plained. They were not associated with relapses of either the mucocutaneous or the pulmonary lesions and they could not be ascribed to sulfadiazine sensitivity. They may have been due to residual bacterial infection of the skin or lungs.

This patient was admitted one month after the patient mentioned in Case I and to the same medical service but the two patients came from different parts of the city and had no possible contact with each other. In the first patient, there was a high titer of psittacosis antibodies demonstrated by the complement fixation test during the second (or possibly third) week of the disease but there was no earlier serum available for comparison, no significant rise in titer one week later and no history of exposure to birds could be elicited. In the present case there was a definite history of handling a dead pigeon eight days before the first symptom of any illness and a constant and significant rise in psittacosis antibody was demonstrated in the patient's serum over a period of five weeks followed by a slight fall one month later. There was

for the presence of a virus in any of the materials studied in these two cases, the methods used and the observations made did not entirely exclude such an occurrence. These two cases, therefore, suggest the possibility of a common or similar etiology in the form of psittacosis or some similar virus but the evidence available is not entirely convincing.

CASE III. A twenty-four-year old, white, American foundry worker was admitted to the Boston City Hospital December 31, 1942. Six days previously he was suddenly taken with a severe shaking chill which was followed immediately by high fever and within a few hours by substernal pain and cough. Two days later he first noticed soreness of the mouth, a sore throat and dysphagia. A physician was called and prescribed a sulfonamide drug in doses of 1 Gm. every four hours on the first day and 0.5 Gm. every hour thereafter. On the following day he developed a severe headache, began to have dysuria and his sputum became slightly bloody. Two days before entry his eyes became very sore and sensitive to light. At that time he noticed a rash on his hands and abdomen. All



FIG. 8. Case III. X-rays of the chest on third (A) and seventeenth (B) hospital days.

his symptoms became progressively worse until he was sent to the hospital.

He had suffered from a skin ailment similar to the present one at least three times in the previous ten years but was never as severely ill with the previous attacks. His most recent episode was in 1940 when he was treated at the Peter Bent Brigham Hospital. At that time he gave a history of sensitivity to sea foods, strawberries and tomatoes manifested usually by diffuse erythematous rash. His white blood counts there were 5,000 to 6,000 with 64 per cent polymorphonuclear neutrophils and 5 to 7 per cent eosinophils; no abnormal findings were made out in the lungs. X-rays of the chest showed only slightly increased lung markings; a biopsy of one of the skin vesicles was done and a diagnosis of erythema multiforme was made. He received no sulfonamide drugs at that time.

On entry the patient was acutely ill, uncomfortable but fully oriented. His temperature was 103°F. and he was slightly dyspneic and cyanotic. On the skin of his extremities, trunk and penis there were numerous round and oval pink lesions varying in diameter from 3 mm. to 2 cm. Some of them had vesicular centers. The scleral and papebral conjunctivae were diffusely swollen and injected and there was marked photophobia. The lips and the skin around the nares were also swollen and covered with dried and cracked bloody scabs. The tongue was coated with thick purulent material and the buccal and pharyngeal mucosae were inflamed and tender and covered with dirty, yellowish-

gray exudate. There were a few scattered rhonchi and crackling râles throughout the lungs. There were no palpable lymph nodes and no other abnormal physical findings were made out.

The white blood cell count on entry was 12,250 but dropped to 8,400 on the third day and thereafter ranged from 3,100 to 6,200, with polymorphonuclears dropping from 91 to about 80 per cent. The blood hemoglobin was 100 per cent on admission and 85 per cent after the third day. Several urine specimens were all acid and their specific gravity ranged from 1.020 to 1.030; all contained 1+ to 3+ albumin and occasional white blood cells; the first ones had a few and the rest numerous red blood cells in the sediment. Only a trace of sulfonamide was detected in the blood on admission. Successive x-rays of the lungs showed increasing areas of mottled infiltration finally involving both lung fields except the extreme apices. (Fig. 8.) Smears of the sputum showed it to be loaded with polymorphonuclear cells but almost no organisms were seen. Cultures of the sputum at first showed only alpha hemolytic streptococci, but later ones showed increasing numbers of hemolytic *Staph. aureus* and beta hemolytic streptococci. Several blood cultures were negative. The blood Wassermann and Hinton tests were negative. Complement fixation tests for psittacosis were negative on January 2nd, 11th and 18th. The cold agglutinin titer of the serum was less than 1:4 on January 2nd and 4th, 1:8 on January 11th, 1:32 on January 15th and

finally dropped again to less than 1:4 on January 18th.

The patient was given 5 Gm. of sodium sulfathiazole in saline intravenously at the time of admission but no further sulfonamide therapy was used. Treatment otherwise consisted of

albuminous precipitate and a few polymorphonuclear cells and fibrin, except in its periphery where the polymorphonuclear cells were particularly numerous. The cells of the inferior surface of the epidermis covering the vesicle were necrotic and were invaded by polymuclear

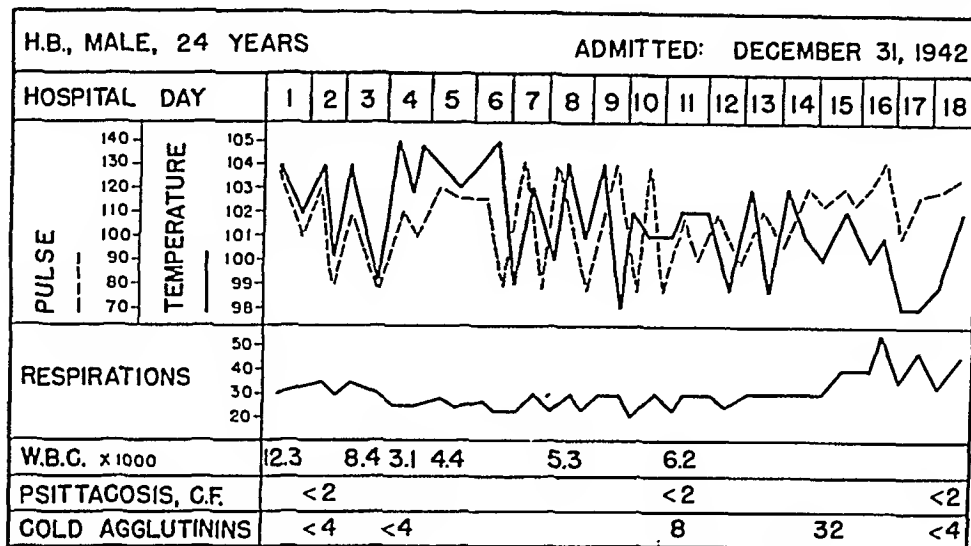


FIG. 9. Clinical chart and certain relevant data in Case III.

frequent sedation, fluids and feedings given parenterally and by mouth with vitamin supplements. Oxygen was given by a tent after the third day. Various types of dressings were applied to the skin lesions without much effect.

The patient's condition continued to get worse during the first few days in the hospital. The skin lesions became frankly bullous in character on the hands and then on the forearms and upper arms. Numerous smaller lesions appeared on the thorax, abdomen, thighs and feet and these also increased in size. Dyspnea and cyanosis likewise increased progressively in spite of oxygen therapy. He became disoriented on the second day and remained so for about a week during which time the signs and symptoms of diffuse pulmonary involvement increased progressively. After the ninth day the patient appeared to improve perceptibly over a period of three or four days. Thereafter, however, the pulse and respiratory rates rose again; dyspnea and disorientation increased; the patient grew steadily more cyanotic and the signs of pulmonary infiltration increased until he died on January 18th. The clinical chart is shown in Figure 9 and the skin lesions in Figure 10.

A biopsy of one of the skin lesions was obtained during the first week. Microscopic sections (Fig. 11) showed a vesicle which contained

and large mononuclear cells. The base of the vesicle consisted of the connective tissue of the corium and was covered in places by fibrin. This connective tissue showed a perivascular infiltration of lymphocytes and an occasional plasma cell. There was a similar infiltration about the coil glands.

Autopsy was performed fifteen hours after death. There were bullous lesions of different ages, most numerous over the arms and legs and over the shoulders and neck. The most recent were light brown, vesicular, rather well circumscribed and contained thin, colorless fluid. Some of the lesions were dry; others were covered by large crusts. The older lesions were darker in color and somewhat scaly. All measured approximately 1 cm. in diameter. The eyelids were swollen and the conjunctivae were injected. The lips were fissured, hemorrhagic and appeared to have been blistered. The scrotum was covered with confluent, bullous lesions. The glans penis showed a moist, hemorrhagic surface with complete loss of epithelium.

All the pleural surfaces were covered by a thin layer of fresh, yellow, fibrinous exudate most marked over the upper lobes. The left lung weighed 1,145 Gm.; the right, 1,675 Gm. The external surfaces of the lungs were deep blue-red with a hemorrhagic appearance along

the posterior surfaces. The lungs were firm, subcrepitant and in some areas non-crepitant. Upon section the cut surfaces oozed a large amount of blood and appeared nodular. These military nodular areas were slightly raised, yellow-white against a blue to gray-red background. They appeared to be purulent but no pus could be expressed. A small amount of yellow, purulent material could be expressed from some of the smaller bronchioles. The bronchi and trachea were covered with a dark red, slimy exudate containing much blood, and the mucosal surfaces were hemorrhagic. The tracheobronchial lymph nodes were enlarged, measuring 2.5 cm. in diameter.

There was a small amount of red-brown, bloody material in the stomach; the gastrointestinal tract was otherwise entirely negative. The pelvis of the right kidney was red-purple and contained a few drops of thick, yellow purulent material near the inferior calyx which contained similar pus. The ureter of this kidney was slightly dilated but no site of obstruction was found. The left kidney was negative. The bladder was boggy, slightly thickened, contained 50 cc. of clear urine and showed several submucosal hemorrhages. The brain appeared normal.

In sections from the right upper lobe (Figs. 11 and 12) some alveoli contained albuminous precipitate but the majority contained desquamated alveolar lining cells and large mononuclear cells. Other alveoli contained some polymorphonuclear leukocytes, many contained old fibrin in which there were masses of cocci and in some there was hyaline membrane formation. In places the alveolar lining cells were swollen and occasional mitotic figures were present. The bronchioles contained polymorphonuclear and large mononuclear cells and cocci. There was marked peribronchiolar infiltration of plasma cells. The septa showed edema.

In sections from the left upper lobe some alveoli were empty and markedly distended; a few were filled with precipitated albumin but the majority contained an exudate of desquamated alveolar lining cells, many of which were vacuolated. In some alveoli there were also masses of old fibrin, some of which was undergoing organization. The alveolar lining cells were swollen and occasional mitotic figures were seen. An occasional bronchiole was filled with polymorphonuclear leukocytes, large mononuclear cells and cocci. There was a marked



A



B



C

FIG. 10. Case III. Appearance of the lesions on the trunk, hand and penis (A), nose, eyes and lips (B) and feet (C) at the time of death.

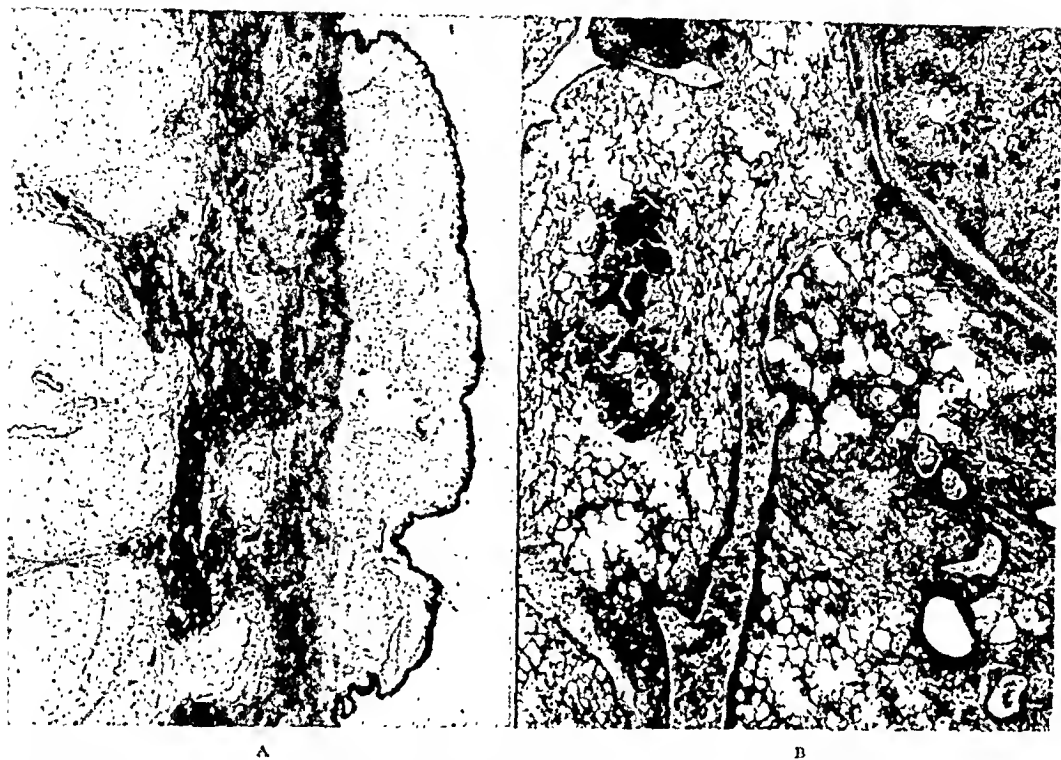


FIG. 11. Case III. A, section of skin obtained by biopsy during the first week ($\times 8$). B, section of lung showing patchy distribution of lesions ($\times 25$).

perivascular and peribronchiolar infiltration of plasma cells and also there were many such cells in the alveolar walls and in some places in the alveolar lumens.

Sections from the left lower lobe were essentially similar to those from the left upper lobe, but in one area there was extensive abscess formation with an exudate of polymorphonuclear cells and numerous cocci. Adjacent to this area was a focus of gangrene in which numerous cocci and bacilli were present. One bronchiole had lost its epithelium and its denuded surface was covered with polymorphonuclear leukocytes and fibrin. There was a perivascular and peribronchial infiltration of plasma cells and some lymphocytes. The pleura was covered with a thin layer of fibrin. The trachea was congested and there was an infiltration of the submucosa and around the glands of plasma cells.

There were numerous plasma cells in the pulp of the spleen. The sinuses of a lymph node contained macrophages which were often phagocytic and there was an increased number of plasma cells in the lymph cords. The bone marrow was hyperplastic and evidenced some lack of maturation on the part of the leukocytes.

There was some infiltration of the connective tissues of the kidney pelvis with lymphocytes and plasma cells. At this site there was also some

fibrin in the blood vessel walls which were infiltrated with a few polymorphonuclear leukocytes.

The cerebral meninges contained a few lymphocytes, large mononuclears and plasma cells.

A culture of the heart's blood was contaminated, but cultures of the left upper lobe and the right upper lobe yielded beta hemolytic streptococcus and hemolytic *Staph. aureus*.

Comment. The illness of the patient in Case III began suddenly with a shaking chill, fever, cough and substernal pain—symptoms characteristic of tracheobronchitis and pneumonia. The sore mouth and throat and the dysphagia began two days later and presumably reflected the development of mucous membrane lesions before that time. The sulfonamide was given only after these symptoms appeared. The skin lesions, the dysuria—which reflected involvement of the urethral meatus—the sore eyes and photophobia all followed. The history of recurrent similar attacks and of erythematous eruptions following ingestion of certain types of food suggest a possible allergic basis for the skin and mucous membrane

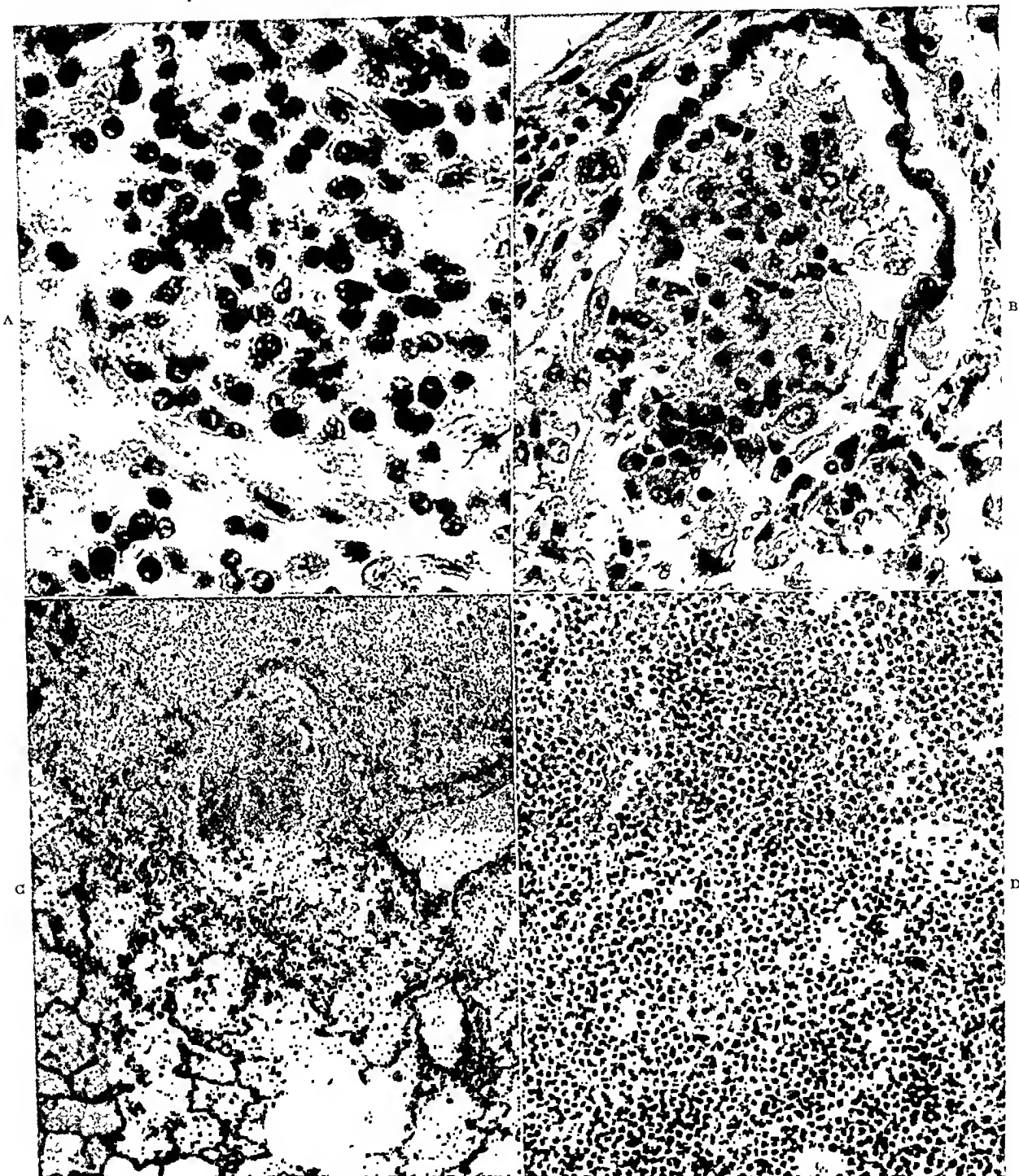


FIG. 12. Microscopic sections of lung showing various types of lesions in Case III. A, interstitial infiltration of alveolar walls with plasma cells ($\times 425$). B, alveolar exudate of mononuclear cells, swelling and proliferation of alveolar lining cells ($\times 350$). C, polymorphonuclear exudate within lumen of bronchiole; mononuclear cells in bronchial walls and in surrounding alveoli ($\times 100$). D, abscess formation with destruction of alveolar walls ($\times 200$).

lesions.* As far as could be ascertained, however, the patient had taken no drugs nor any food to which he was known to be sensitive before the onset of the present episode. Also there was no known exposure to any sick birds or animals or to any infections other than the usual respiratory infections that were prevalent at the time. The exact etiology in this case, as in almost all other similar cases that have been reported, remains obscure.†

In contrast to Case 1, in which sulfonamides were given throughout most of the course, these drugs were omitted soon after entry in this patient chiefly because it was thought undesirable to risk the consequences of sensitization. Serious infection with *Staph. aureus* and *Streptococcus hemolyticus* occurred and extended down the bronchial tree and into the pulmonary parenchyma. It was manifested by necrosis of some bronchial walls and abscess formation. Such a reaction was not seen in Case 1.

The underlying disease in the lungs, however, was similar in both cases and was characteristic of a non-bacterial type of reaction. In this case, as in the previous one, no elementary or inclusion bodies were seen in the sections of the skin, lungs and other tissues, and attempts to isolate a virus from the bullous fluid and from suspensions of the lung by inoculation of mice and embryonated hen's eggs all failed.‡

CASE IV. A nine-year old white boy was well until April 17, 1943 when he first complained of mild headache and lassitude. His face appeared flushed at the time, but two days later his temperature was 104°F., he became drowsy and delirious and developed a rash on the face and upper trunk consisting of raised, bright red areas. These gradually extended, became confluent and numerous large blisters appeared on the face, trunk and extremities. His eyelids

* Of interest in this connection is the recent report of a recurrence of Stevens-Johnson's disease in which some of the symptoms were apparently improved by treatment with benadryl.²¹

† A virus serologically related to herpes was isolated from the lung of this patient after this paper was submitted for publication. The exact relation of this virus to the pulmonary and mucocutaneous lesions is still uncertain.³⁰

became swollen at that time. Of interest is the fact that the patient's mother found a dead sparrow in his room on that day and heard him mutter about a bird in his delirium. From his playmates it was later learned that the patient had been nursing the sick sparrow at home in his room for several days and that it had died and he was preparing it for a formal burial just before he became ill. There were no other details of this exposure and none of the playmates were known to have become ill.

When the patient was admitted to the South Department on April 21st, he appeared extremely ill, semistuporous and breathing with labored and grunting respirations. His eyes were closed by the intense edema of the lids and there was marked conjunctivitis. The pharynx was deeply red, the tonsils enlarged and there were many deep red macular areas on the buccal mucous membrane, some of them with central vesicles or bullae. There was a diffuse morbilliform, non-blanching rash over the body surface, more marked on the upper part of the trunk, with many large bullae within the areas where the maculopapular lesions had become confluent. The epidermis over some of the bullae had been removed in several areas leaving a raw, moist hemorrhagic surface. A few small shotty nodes were felt in the cervical and axillary regions. The lungs were resonant throughout; many coarse rhonchi were heard over the right lung and a few crepitant râles over the left lung but no signs of consolidation were made out. A soft, systolic murmur was heard over the entire precordium. The white blood count was 8,400 with 82 per cent polymorphonuclears. A blood culture yielded no growth.

The patient was given bland local application to the lesions of the skin and mucous membrane, intravenous fluids, nasal oxygen and calcium gluconate for some tremors which were noted soon after admission. Dyspnea and cyanosis increased progressively and the rhonchi became louder and more numerous. The tremors recurred frequently and early on the following morning the patient had a convulsive seizure and died shortly thereafter.

Autopsy was done five hours after death. The lesions of the eyes, skin and mucous membranes were essentially as already described. (Fig. 13.) There were no genital lesions. The pleural surfaces were free, smooth and glistening. The lungs were slightly increased in weight, the



FIG. 13 Case iv. Lesions of the face and upper trunk (A) and closer view of lesions of upper arm (B) at time of death.

right weighed 225 and the left 200 Gm. They appeared red, hemorrhagic and subcrepitant. Section of the lung revealed hypostasis of the lower lobes and several slightly depressed, dark-red areas 1 to 1.5 cm. in diameter. A frothy exudate could be expressed from the cut surfaces. The rest of the organs appeared normal.

Microscopic sections from all lobes of the lungs showed many normal alveoli and others containing an albuminous precipitate. A few bronchioles contained polymorphonuclear leukocytes and masses of cocci and bacilli. Sections from the right middle and both lower lobes also showed marked congestion and some plasma cells in the alveolar walls. In those from the right lower and left upper lobes there were a few alveoli which showed acute lesions with fibrin and polymorphonuclear cells in the alveolar walls.

A section of a skin vesicle showed its contents to consist of a few polymorphonuclear leukocytes, numerous mononuclear cells with nuclei that were often lobulated and contained heavy chromatin. There was necrosis of all but the superficial layers of the epidermis. The base of the vesicle consisted of connective tissue infiltrated with lymphocytes, macrophages and occasional plasma cells and mast cells. The other organs were essentially normal. A culture of the heart's blood showed no growth.

Tests done on serums obtained on admission and at autopsy were negative for psittacosis antibodies and for cold agglutinins. Inoculation of vesicle fluid and lung suspensions into eggs and mice yielded no recognizable virus.

Comment. In this case there was a fulminating bullous type of erythema involving most of the skin, and the mucous membrane of the oropharynx with conjunctivitis but without involvement of the genitals. There were symptoms and signs consistent with pneumonia but autopsy revealed mostly congestion and edema. There was some bronchiolitis and a few, small, scattered, acute alveolar lesions. There was little if any evidence of any interstitial mononuclear reaction and no characteristic involvement of the alveolar walls similar to that seen in Cases I and II. The case is of interest in relation to Cases I and II because of the history of an intimate and prolonged exposure to a sick bird that had died—in this case a sparrow. There was nothing else to suggest psittacosis but the negative serologic findings are not significant because of the short course of the illness, less than five days. The absence of characteristic lesions in the lungs could also conceivably be the result of this fulminating course.

COMMENTS

The four cases that are reported here all had widespread lesions of the skin and mucous membranes which fit the designation erythema multiforme exudativum. For a discussion of the confused terminology of these and similar dermatologic conditions,

however, the reader is referred to other reports and reviews.^{8,11,22} The full evolution of the lesions was seen only in Case II after recovery; they healed completely without scarring but with slight pigmentation. Furthermore, the ocular lesions of the patient in that case also seemed to heal without apparent scarring and without visual impairment in spite of the ulcerations of the cornea that were seen during the acute stage of the disease. The type and evolution of skin lesions and the extent of involvement was otherwise quite similar in each of the first three cases but in Case II they differed in that the lesions advanced more rapidly, were more exudative in character and did not involve the genitals.

The pneumonia in each of the first three cases likewise was similar in character clinically and roentgenographically, except for the terminal increase in the extent and density of the lesions as seen by x-ray in the third patient, which resulted from the superimposed bacterial infection. These pneumonias resembled the severe cases of primary atypical pneumonia with extensive bilateral miliary type of involvement. The findings in Case III, moreover, correspond to those found in a similar case of primary atypical pneumonia complicated by staphylococcal infection.²³

The gross and microscopic findings in the lungs also corroborated the clinical picture and was characteristic of a non-bacterial type of reaction. There was a patchy miliary type of lesion which consisted histologically of (1) an interstitial infiltration with various kinds of mononuclear cells, predominantly plasma cells, (2) swelling of the alveolar lining cells with occasional mitoses and (3) an alveolar exudate consisting usually of large mononuclear cells and desquamated alveolar living cells but in some areas containing only precipitated albumin and red blood cells.

Lesions containing much fibrin and many polymorphonuclear leukocytes, which are characteristic of an acute bacterial reaction, were rare. They were found in Case III in which there was also some ulceration of the

bronchiolar mucous membrane and areas of abscess formation in the parenchyma. In Case I, however, the cellular infiltration of the bronchiolar walls was a mononuclear one, in spite of the presence of a purulent exudate with bacteria in their lumens, and the same was true in most areas of the lungs in Case III.

These findings are also similar in many respects to those described in cases of psittacosis²⁴⁻²⁷ except that in the present cases there was less fibrin and red blood cells in the alveoli, the lesions were more discrete and more diffusely scattered throughout the lungs, the interstitial infiltration was more predominant and no inclusion bodies were seen.

There was a striking difference between the rather mild response to secondary infection with staphylococcus in these patients when compared with the severe and extensive type of ulceration and necrosis that occurs under similar conditions in the trachea, bronchi and lungs infected with influenza virus.^{28,29} A comparison of the findings in Case I with those in Case III nevertheless suggests that there is some virtue in antibacterial therapy in severe cases in spite of some feeling that, in patients with primary atypical pneumonia at least, there is a relative resistance of the lung to bacterial infection. The use of penicillin in these cases would have been preferable to the sulfonamides because of the predominance of staphylococci and the greater effect of the antibiotic on those organisms. It may be said, however, that while the bacterial infection may have been a determining factor in the fatal outcome in Case III the same was certainly not true in Case I.

The history of exposure to dead birds in Cases II and IV, the high titer of psittacosis antibodies in Case I and the significant rise in titer of such antibodies in Case II are of particular interest. These findings suggest the possibility of infection with a psittacosis-like virus transmitted from birds. Unfortunately, no virus was isolated from materials obtained from these patients. The significance of cold agglutinins in patients with

primary atypical pneumonia is not known but high titers or rises in titers of cold agglutinins have not been reported in proved cases of psittacosis. If Case I and II are indeed cases of psittacosis, then it will be necessary to consider that a cold agglutinin response may occur in some cases of this disease as it often does in cases of primary atypical pneumonia in which psittacosis had been excluded. The unlikely alternative would be to consider that two types of non-bacterial pneumonia coexisted.

There is no evidence to implicate psittacosis in Case III. In that case there was a rise in the titer of cold agglutinins, although not to a high level, and no psittacosis antibodies were demonstrated.* Case IV is included because of the striking skin lesions occurring after what may have been an intimate and prolonged exposure to a sick bird that died. There was no characteristic pneumonia, no virus was isolated and the patient died before any serologic response could be expected.

In connection with these cases some of the skin lesions described by Simpson in cases of psittacosis seen in England²⁴ are of interest. He observed "rose spots" or similar skin lesions in nine patients, usually between the ninth and thirteenth day of the disease, sometimes in successive crops and always on the trunk. They consisted of small, red maculopapules often surrounded by a white halo with a thin, red line bounding this like a planet. Of other skin lesions sudamina were not uncommon, roseola and erythema occasionally occurred and herpes labialis was present in 5 per cent of his patients.

SUMMARY

Four cases of erythema multiforme exudativum are reported; three of them were fatal and the autopsy findings are presented.

There was a diffuse miliary type of pneumonia in two of the fatal cases and in

the one with recovery. The pneumonia in these patients resembled that of the severe and diffuse type of primary atypical pneumonia of unknown etiology in every respect—clinically, roentgenographically and pathologically; it resembled that of psittacosis in many respects. In one of the fatal instances there was a significant amount of secondary bacterial infection.

Evidence suggesting a possible infection with a psittacosis-like virus was obtained in three cases. In Case I there was a significantly high titer of antibody for psittacosis virus demonstrated by complement fixation. In Case II there was a significant rise in titer of such antibodies during the course of the illness and a history of contact with a dead pigeon eight days before the first symptom. In Case IV there was only a history of contact with a sparrow during its fatal illness. The latter patient died on the fifth day of his disease and the lungs showed only a few acute focal lesions in the alveolar walls. No virus was isolated from any of the patients.

Cold agglutinins were demonstrated in high titer in the serum of the patient in Case I and appeared during the course of the illness in the patients in Cases II and III.

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Addendum: Two additional cases of extensive pneumonia and severe erythema multiforme exudativum which resembled Cases I and II clinically were observed recently at the Massachusetts General Hospital through the courtesy of Drs. Greene, FitzHugh and Arlie V. Bock. Neither patient gave a history of exposure to birds. Both recovered and developed high titers of cold agglutinins but no psittacosis antibodies during convalescence.³⁰

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Differential Diagnostic Problems in Acute Pulmonary Embolization

IRVING R. ROTH, M.D.

New York, New York

ACUTE pulmonary embolization is a dramatic clinical syndrome of equal interest to both the physician and the surgeon. The disease compels attention for several reasons. Postmortem studies have revealed that a large number of cases escape clinical detection. Clinical experience, on the other hand, has taught that not only is diagnosis and treatment, at times, difficult but that the mortality rate is very high. Pulmonary embolization confounds diagnosis most commonly at the hands of those who are not fully aware of circumstances predisposing to it, or at the hands of those who are not familiar with the diverse clinical syndromes in the guise of which this disease may masquerade.

The following case history is an example of the confusion that may result and the diagnostic difficulties that may ensue in a case of pulmonary embolization.

CASE REPORT

A forty-nine year old man suffered an acute attack of dyspnea, went into shock and finally collapsed while waiting for his train at a railroad station. An ambulance took him to a hospital of a nearby industrial town. The patient's wife informed the admitting physician that her husband was a "cardiac," having had "angina" which dated to an acute coronary thrombosis three years prior.

On admission, examination revealed dyspnea, fever, leukocytosis and an increased sedimentation rate. Electrocardiographic studies showed auriculoventricular dissociation (the ventricular rate was 65 a minute and the auricular rate 103 a minute); QRS complexes widened to 0.12

seconds and heavily slurred, especially in their terminal portions; deep S waves present in leads I and II; T waves shallow in leads II and III; R₄ absent. The pattern was that of a complete auriculoventricular heart block and an atypical right bundle branch block. (Fig. 1 A.)

Diagnosis was recorded as an acute recurrent coronary thrombosis or an acute coronary insufficiency. Treatment consisted of complete bed rest, oxygen and sedatives.

Two and one half weeks after admission, while the patient was still in bed but symptom-free, he had another attack of severe dyspnea and a bout of fever which went up to 103°F. Bedside x-ray at this time revealed pulmonary changes which prompted the diagnosis of an intercurrent bronchopneumonia. Penicillin was administered, the symptoms abated and the "lungs cleared" within a week.

During the fourth week the patient suffered a third acute episode, with his temperature rising to 104°F. Symptoms were predominantly cerebral. Cheyne-Stokes respiration, an aphasia and a transient paralysis of the right side of the body were noted. The diagnosis of a "cerebral accident" was made and the probability of a thrombotic or embolic episode was entertained.

Except for the aphasia, cerebral symptoms gradually cleared. A low-grade fever, however, persisted and toward the end of the fifth week the temperature again rose to 104°F. Purpuric spots appeared at both elbows. At this time the diagnosis of a bacteremia was considered and in spite of repeatedly negative blood cultures intensive penicillin therapy was instituted.

Since diagnosis was doubtful, the therapy of no avail and since a guarded prognosis had been given, the patient's family, in a desperate hope for additional facilities, laboratory studies and medical consultations, insisted that a transfer be

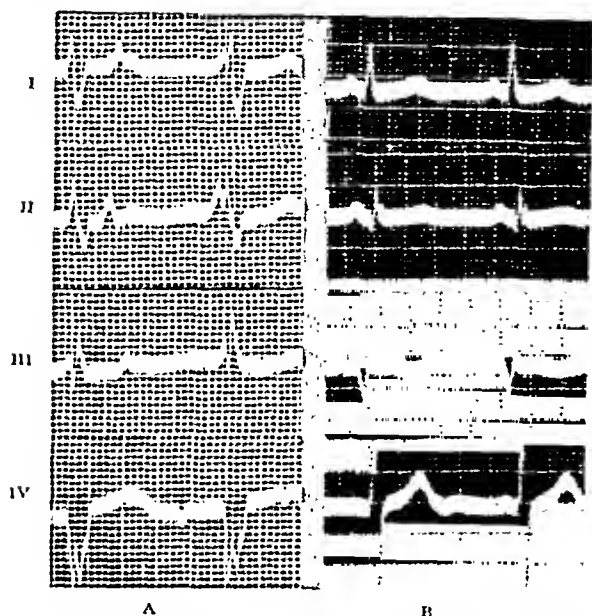


FIG. 1. Electrocardiograms recorded in a patient with an acute pulmonary embolization, who, three years prior had a coronary occlusion with posterior wall infarction. A, tracings taken on day of collapse with pulmonary embolization; B, tracings taken three years prior in the course of convalescence several months after the coronary occlusion.

made to a larger hospital. Accordingly, the patient was transported to a hospital in New York City.

On readmission the patient appeared cachectic, as if he had weathered a protracted siege. He was acutely ill, mentally confused, pale, febrile and dyspnoic. The heart action was regular; the rate was 100 to 120 a minute. The systolic blood pressure was low, 85 to 100 mm. Because of the patient's critical condition auscultation of the lungs was difficult. However, signs of pulmonary consolidation were detected in the lower portion of the left lung and upper portion of the right lung, posteriorly. Except for distention, the abdomen was normal. There were extensive purpuric areas over both elbows. A bedside x-ray of the chest showed cardiac enlargement and infiltration of the upper and lower portions of the right lobe and the basal portion of the left lobe. It was not possible to state from the x-ray findings whether the pulmonary processes were due to pneumonia or lung infarctions. A blood count showed 34,000 leukocytes with 92 per cent polymorphonuclears. The cells showed marked toxic granulation. The fever ranged between

102 to 103°f. Respiration was between 40 to 50 a minute. There were evidences of circulatory failure. The patient died forty-eight hours after admission.

The autopsy revealed arteriosclerotic heart disease with hypertrophy and dilatation of both ventricles; an old occlusion with recanalization of the right coronary artery; an old occlusion of the anterior descending branch of the left coronary artery; aneurysmal dilatation of the left ventricle; fibrosis of the interventricular septum and recent occlusion of the left anterior descending and the left circumflex coronaries with a mural thrombus in the left ventricle. Multiple bilateral pulmonary emboli with pulmonary infarctions were found in all lobes.

The cause of death was determined as extensive pulmonary embolization and congestive heart failure.

This unusual case forcibly illustrates how far afield one may be led by a case of pulmonary embolization. Acute coronary thrombosis, bronchopneumonia, cerebral accident and subacute bacterial endocarditis were successively diagnosed in the course of an illness of approximately five weeks' duration.

Autopsy, to be sure, disclosed extensive coronary artery disease with several old occlusions and myocardial fibrosis. There was also a "recent" occlusion of a left coronary artery with a mural thrombus in the left ventricle, which at a glance, might seem to account for the embolic phenomena. This, however, cannot be accepted as a probable cause of the pulmonary lesions in this patient. Emboli from the left side of the heart find their way into the systemic and not into the pulmonary circulation. In view of the fact that pulmonary embolization was extensive, involving all lobes, upper as well as lower, without any significant embolization of other viscera or the extremities, it is reasonable to assume that the heart was not the source of the embolization in this instance and that the source was not revealed by the autopsy.

Pulmonary embolization, of course, is not an uncommon complication of organic heart disease, especially coronary thrombosis. Estimates in this connection vary widely, anywhere from 3 per cent in clinical series to 42 per cent in postmortem series. Many small emboli detected at autopsy undoubtedly produce few, if any, clinically discernible symptoms. Mild symptoms when present are readily obscured by symptoms of heart disease of which pulmonary embolization is a complication. Emboli arising in the left ventricle may lodge anywhere in the systemic circulation. They commonly affect the spleen, kidneys and brain, less often the mesenteric arteries or the vessels of the extremities. In this condition pulmonary emboli are rare, and when they do occur they are but a part of a widespread systemic embolization. With right ventricular thrombi, on the other hand, pulmonary embolization is common. According to Bean¹ as many as 75 per cent of patients in this group have pulmonary emboli.

Bean's observations, based on morphologic studies, no doubt included many cases that were not severe enough to be clinically recognized. This would imply that cardiac emboli are not necessarily productive of massive pulmonary lesions. Bean stated, in fact, that in every one of his patients in whom massive pulmonary embolization had occurred and caused death, the emboli had arisen not from the heart but from distant sources such as veins of the pelvis or lower extremities.

A series of one hundred consecutive cases of coronary occlusion were studied by Nay and Barnes² for types of thrombotic and embolic phenomena. Among thirty-seven patients who exhibited such complications, fourteen were diagnosed on clinical criteria as having had pulmonary embolism. It was the direct cause of death in only one patient but it seemingly contributed to the death of five others. Autopsy on these six patients re-

vealed that four had mural thrombi in the right auricle or ventricle. Thrombophlebitis was noted in three of the fourteen cases diagnosed as having pulmonary embolization. Embolization occurred as early as the fifth day in one patient. In all others, it occurred between the sixteenth and thirty-seventh day.

Among surgical patients pulmonary embolization is said to occur in only $\frac{1}{2}$ to 3 per cent of instances.³ This seemingly low incidence is greatly overshadowed by the incidence encountered among patients with well defined heart diseases. The significance of pulmonary embolization as a surgical complication might be lost if it is not realized that this condition is, nevertheless, responsible for 6 per cent of postoperative deaths.^{3,4} Surgical patients are precisely the ones in whom diagnosis is important. Chronic cardiacs carry a certain amount of hazard by virtue of their heart disease. Pulmonary embolization is only one of many serious complications to which they are vulnerable. In surgical patients, on the other hand, in whom the source of the embolization is not a cardiac chamber but more commonly a surgically approachable site amenable to eradication, the diagnosis of pulmonary embolization is all the more important. It may be the only major factor in prognosis.

The detection of pulmonary embolization is at times admittedly difficult. However, there is an immediate lead in the realization that it is a disease of the bedridden, the convalescent and the inactive. In the majority of instances it is due to a thrombophlebitis in some portion of the venous system not associated with the portal circulation. Thrombophlebitis of the deep veins of the lower extremities has been regarded as the most common source. Superficial varicose veins, at times suspected, are perhaps of little importance; in these circulation is retrograde, peripheral and not central.

Reporting on eighty-six fatalities among 304 patients with hip fracture, Goladner, Morse and Angrist⁵ encountered pulmonary embolization in nine out of twenty-five patients that came to postmortem examination. This constituted 36 per cent of autopsy material and somewhat over 10 per cent of all fatalities. They were impressed with the rôle of the femoral veins as sources of emboli to the point where they advocated prophylactic bilateral ligation in patients who were unlikely to become ambulant at an early date. In contradistinction, Bosworth and his associates, in a series of one hundred patients with trochanteric fractures in whom, because of reduction and the use of Jewett nails minimal bed rest was required, encountered only one patient with pulmonary embolization.⁶

A striking example of the influence of the length of bed rest on the production of pulmonary embolization is presented by Ask-Upmark.⁷ In an analysis of 1,454 patients with lobar pneumonia treated in the course of twenty-six years, thromboembolism was observed in only twenty-seven, approximately one out of fifty. More than three-fifths of all cases occurred among persons over forty years of age. They made the interesting observation that with the advent of specific serum therapy during the final four years of their study, more patients with thromboembolism were encountered than during all of the preceding twenty-two years. This they assigned to the survival of patients who otherwise would have succumbed and who, having survived, constituted a large number of added convalescents. An average time of about two weeks elapsed between the onset of pneumonia and thromboembolic phenomena.

Consideration of the pathogenesis of pulmonary embolization yields valuable diagnostic and therapeutic hints. As already stated the source of an embolus may be any portion of the venous system not draining

the portal system, thrombophlebitis of the deep veins of the lower extremities being the most common. An embolus dislodged from such a source may locate in any portion of the pulmonary arterial tree and infarction of the lung may result. Often, however, there is no infarction. For the development of an infarct the venous return from the lung it would seem must also be obstructed. Emboli may arrive singly or in showers. Each clinical episode does not necessarily represent a separate embolization. On the other hand, it is not uncommon to find several pulmonary zones of embolization at autopsy in patients who had only a single major clinical episode.

The onset of the clinical picture in some patients with pulmonary embolization may be insidious, or at best, may present but few symptoms. A secondary rise in temperature or an area of lung consolidation without specific bacteriologic findings should always arouse suspicion. Extension of the embolus into larger channels producing massive embolization usually gives rise to major clinical patterns which often simulate other acute diseases and thus create difficulties in diagnosis.

Regardless of the clinical pattern which it may simulate, a major episode of pulmonary embolization is generally ushered in by some measure of vasomotor shock. Fever, dyspnea, rapid thready pulse, low blood pressure, leukocytosis and an increased sedimentation rate are common to all patterns. Leading symptoms may point to diseases such as acute pulmonary, gastrointestinal, cerebrospinal or cardiovascular syndromes. The reason for such divergent and dramatic manifestations is inherent in the mechanism of pulmonary embolization.

As a result of sudden massive obstruction of a portion of the pulmonary arterial tree, for example, respiratory embarrassment usually takes place. This may vary from a simple tachypnea to an agonizing asphyxia.

Cyanosis is often marked. Regional pleuritic pain, its location depending upon the zone of pulmonary involvement, may accompany the dyspnea. The chest pain often radiates to the shoulders or the neck. X-ray of the lungs may show an area of consolidation due to infarction. Such symptoms and findings, together with fever, leukocytosis and increased sedimentation rate, all of which usually accompany the clinical picture, constitute a pleuropneumonic syndrome.

Shock, being a common initial symptom in massive pulmonary embolization, may if protracted produce a cerebral anoxemia to a degree that leading symptoms will point to the brain and not to the lungs. Faintness, for example, may be an early symptom; syncope and convulsions at times follow. If, as usually happens, there is also fever, leukocytosis and an increased sedimentation rate, the clinician for the time being may be hard-pressed to rule out an acute cerebrospinal syndrome.

As a result of shock, marked imbalance of the sympathetic nervous system may take place. Vagus reaction not being adequately opposed may be severe. Acute abdominal pain may be a leading symptom, severe enough at times to suggest an acute visceral crisis. In addition to the abdominal pain, vasomotor shock, fever, leukocytosis and the increased sedimentation rate a mild jaundice may also be present. In acute pulmonary embolization the icteric index is often increased, probably as a result of an acute hepatic anoxia. While such a gastrointestinal syndrome is an uncommon manifestation of an acute pulmonary embolization, it should always be thought of by both the surgeon and the physician.

By far the most common and most dramatic complication of pulmonary embolization is right heart embarrassment. As a result of blocking of a portion of the pulmonary arterial bed there is a rise of pressure within

the lesser circulation. This acts as a sudden load on the right ventricle and may produce right heart failure (acute cor pulmonale). If the excessive load persists and if the coronary arteries of the right ventricle are inadequate and cannot supply the functional demands of the overloaded heart, the process culminates in an acute coronary insufficiency with myocardial ischemia. Reflex vasospasm of the coronary arteries may contribute to the discrepancy between supply and demand. Postmortem studies of hearts in pulmonary embolization have disclosed extensive areas of myocardial necrosis, especially of the right ventricle and the interventricular septum.⁸

If, as the case often happens to be, symptoms of cardiac embarrassment such as severe chest pain, dyspnea, rapid heart action, fall in blood pressure and vasomotor collapse dominate the clinical picture of pulmonary embolization, a tentative diagnosis of an acute cardiac episode would seem warranted. The fever, leukocytosis and increased sedimentation rate which accompany the episode strengthen the suspicion and not uncommonly the diagnosis of coronary thrombosis is finally made. Electrocardiograms, always resorted to in such instances, at times aid in the differential diagnosis. At other times they are confusing. Depending upon the degree of right heart embarrassment which it produces, massive pulmonary embolization may itself alter the electrocardiogram. In a way its pattern resembles those seen in coronary thrombosis with posterior wall infarction.⁹ If such an electrocardiogram is read by one whose experience is limited, the clinical diagnosis of coronary thrombosis may be "confirmed."

The importance of a differential diagnosis between acute pulmonary embolization and coronary thrombosis is at once apparent, if it is realized that timely therapeutic measures such as ligation of deep leg veins and the administration of anticoagulants may

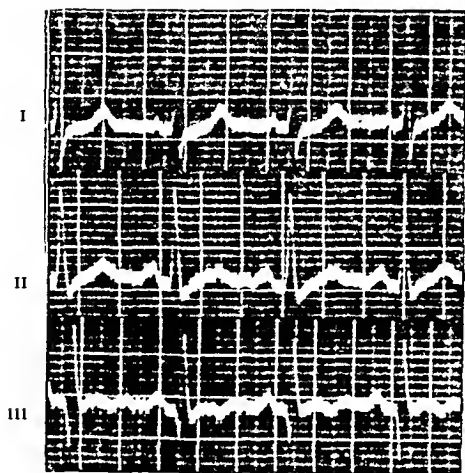


FIG. 2. Electrocardiograms of an "acute cor pulmonale"; standard leads I, II and III taken twelve hours after the onset of an acute pulmonary embolization. (Published by McGINN and WHITE. *J. A. M. A.*, 104: 1477, 1935. They show: "... low origin of the ST interval in lead I and a gradual ascent of the ST interval in lead 2. In lead 3 ... a Q and a definite and late inversion of the T wave."

arrest further pulmonary embolization. To rest on a diagnosis of coronary thrombosis, on the other hand, when treatment is essentially expectant, is to permit serious mischief to carry on without any attempt to curtail its course.

Differential diagnostic criteria between pulmonary embolization and coronary thrombosis with posterior wall infarction, although at times finely shaded, are nevertheless many. The history, for example, is all important. Pulmonary embolization is essentially a disease of the bedridden or convalescent. Furthermore, this disease does not favor either sex. Coronary thrombosis, on the other hand, generally occurs in patients who have been ambulant and the disease is distinctly more common among males.

The onset of the two diseases is different. In pulmonary embolization the onset is often sudden and overwhelming. In coronary thrombosis it is more gradual and significant prodromas precede the critical state by several hours or days. Chest pain in pulmonary embolization is sharp, pleuritic

and has no typical localization. In coronary thrombosis chest pain is pressing or constricting. When severe it is crushing but never sharp or stabbing. Its location is sub-sternal with radiation to the shoulders and arms, especially to the left.

Dyspnea and cyanosis in patients with massive pulmonary embolization are often intense, while in coronary thrombosis they are generally mild or may not be present at all. Shock is frequently a first manifestation of pulmonary embolization. It usually accompanies the chest pain; actually, it precedes it in one case out of three. In coronary thrombosis, on the other hand, shock when present is a culmination of several hours of increasing chest pain. Syncope is not uncommon in pulmonary embolization. It may, in fact, appear as a first manifestation. In coronary thrombosis it is practically never encountered.

Rapid heart action and low blood pressure are early manifestations of pulmonary embolization. They are expressions of vasomotor shock and may accompany or precede the onset of the chest pain. In the early stage of coronary thrombosis, pulse rate, as a rule, is not accelerated and blood pressure is not particularly depressed. The pulse, in fact, may even be slow for several hours after the onset of the chest pain and the blood pressure may rise to unusual heights during the pre-occlusion agony.

Fever, leukocytosis and an increased sedimentation rate appear early in pulmonary embolization and may reach conspicuous heights within several hours. In coronary thrombosis these are late phenomena. They appear twenty-four to thirty-six hours after the onset of major symptoms and, except for the sedimentation rate, seldom reach great heights. An elevated icteric index, common in massive pulmonary embolization, is rarely if ever present in coronary thrombosis.

Chest x-rays, although of little aid during the early stages of pulmonary embolization, may later disclose areas of lung infarction. At times the pulmonary artery may also appear dilated. In coronary thrombosis the x-ray is of limited diagnostic value. The cardiac silhouette is not particularly characteristic. Lung fields may, of course, show passive congestion.

Considerable reliance has been placed in recent years upon the electrocardiogram as a differential diagnostic aid between acute pulmonary embolization and coronary thrombosis. About a decade ago, McGinn and White¹⁰ had called attention to certain features of the electrocardiogram in patients with "acute cor pulmonale." In a study of nine patients with acute cor pulmonale secondary to pulmonary embolization they found significant changes as follows: (1) Prominent S wave and low origin of the T wave in lead I, the S-T segments starting slightly below the base line; (2) a gradual "staircase" ascent of the S-T interval, from the S wave to the T wave in lead II; (3) conspicuous Q waves and a late inversion of the T waves in lead III and (4) in some cases, abnormal direction of the T waves in lead IV without alteration of the QRS complexes. (Fig. 2.) Restoration of the electrocardiograms, they pointed out, may appear in some patients as early as forty-eight hours after the onset. Graphic changes they believed were due to dilatation and partial failure of the chambers on the right side of the heart.

In more recent years, Murnaghan, McGinn and White¹¹ conducting studies on larger groups corroborated previous observations. They regarded the electrocardiographic changes as an expression of an acute cor pulmonale resulting from the pulmonary embolization. Actually, in some of their patients the diagnosis was first suggested by the electrocardiogram.

An additional electrocardiographic pat-

tern of considerable interest has been pointed out by Durant et al.¹² In a study of three patients in whom electrocardiograms were taken within two to six hours after the onset of acute pulmonary embolization, they noted changes characterized by defective intraventricular conduction. Six to twelve hours after the onset normal intraventricular conduction was reestablished and the electrocardiographic pattern of an acute cor pulmonale supplanted the earlier graph. They, therefore, suggested that graphic changes in pulmonary embolization be viewed as (1) early changes, characterized by intraventricular conduction defect of the atypical right bundle branch type and (2) late changes, characterized by the pattern described by McGinn, White and others as representing acute cor pulmonale. Durant and his associates noted, as have others, that electrocardiographic changes in pulmonary embolization tend to disappear by a gradual restitution toward the normal, except for the persistence in some instances of a Q₃ and a negative T₃. Figure 3 B represents early electrocardiographic changes in a patient with massive pulmonary embolization.

It should be emphasized, of course, that strictly speaking the pattern of the electrocardiogram never portrays anatomic defects directly, be it pulmonary embolization or any other. The electrocardiogram records physiologic events only. Anatomic defects are diagnosed by deduction from abnormal graphs but particularly from the clinical picture. It should be remembered, furthermore, that electrocardiographic changes in pulmonary embolization are not consistent and that, even when present, they may be altered by stigmas of pre-existing heart disease. (Fig. 4.) In this connection warning has also been issued by others. Currans, for example, cautioned that "in appraising the electrocardiographic changes during pulmonary embolization, it should be borne in mind that no one electro-

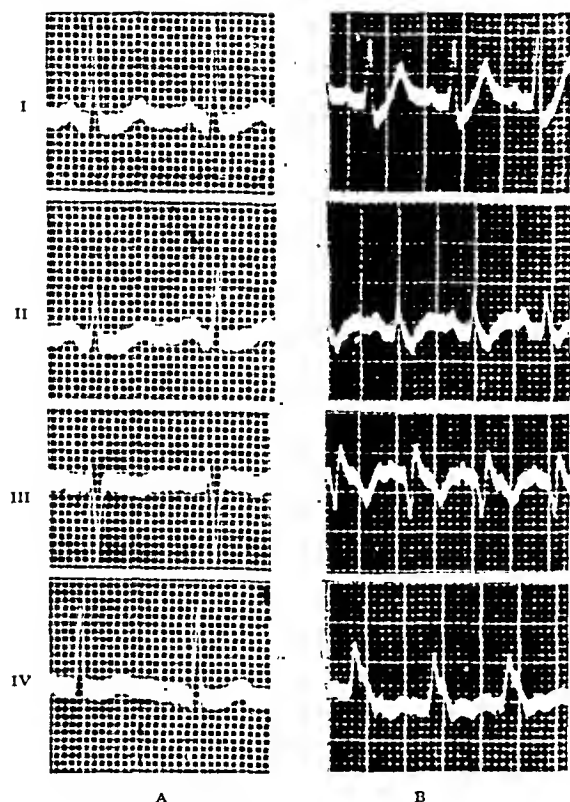


FIG. 3. Electrocardiograms of a fifty-eight year old woman with duodenal ulcer, who two weeks after admission sustained a spontaneous, massive pulmonary embolization. Death occurred within two-and-a-half hours. A, electrocardiograms on admission, essentially normal; B, electrocardiograms taken less than two hours after the onset of the acute episode. They show the "early changes," an atypical right bundle branch block.

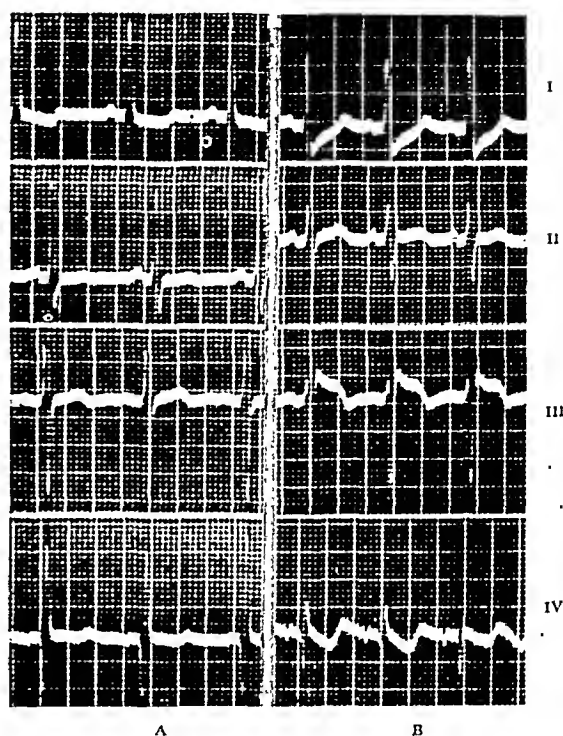


FIG. 4. Electrocardiograms of a seventy-two year old woman with known hypertension, who four days after an abdominal operation developed pulmonary embolization. A, preoperative electrocardiograms showing a pattern commonly encountered in left heart enlargement or left heart "strain." B, electrocardiograms taken twenty-four hours after the onset of pulmonary embolization. The pattern is that of an acute cor pulmonale modified by preexisting heart disease.

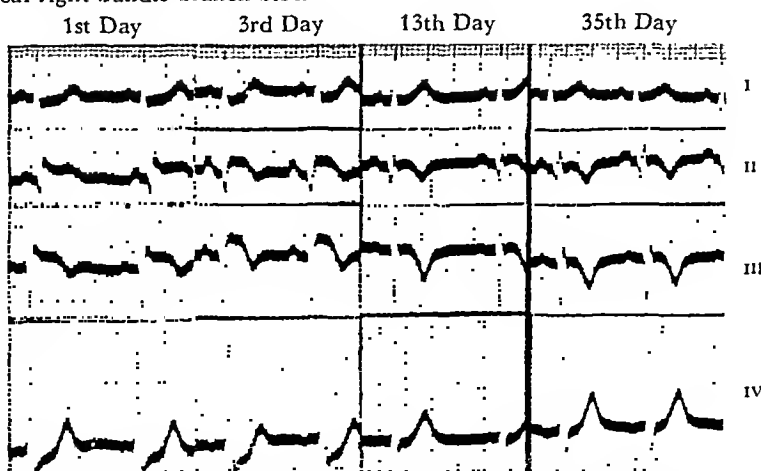


FIG. 5. Electrocardiograms taken consecutively on the first, third, thirteenth and thirty-fifth days in the case of an acute coronary occlusion with posterior wall infarction. The first two tracings (first and third days) represent initial transient patterns, characterized mainly by RST segment deviations. The last two tracings (thirteenth and thirty-fifth days) represent restitution or relatively static patterns, characterized mainly by T wave inversions in leads II and III. Conspicuous Q_2 and Q_3 , present in the earlier graphs persist throughout the restitution patterns of the later graphs.

cardiographic abnormality is consistently present in pulmonary embolization."¹³

In the differential diagnosis between an acute pulmonary embolization and coronary thrombosis the electrocardiogram is of real value nevertheless. An appreciable

or no danger of ever confusing it with the pattern of an acute cor pulmonale.

Whenever the electrocardiograms of pulmonary embolization and coronary thrombosis with posterior wall infarction do resemble each other, the clinical pictures of

TABLE I

COMPARISON OF CLINICAL FEATURES, LABORATORY AND ELECTROCARDIOGRAPHIC FINDINGS IN ACUTE PULMONARY EMBOLIZATION AND IN CORONARY OCCLUSION WITH POSTERIOR WALL INFARCTION

	Acute Pulmonary Embolization	Coronary Occlusion with Posterior Wall Infarction
History.....	Convalescent (medical or surgical)	History of angina on effort
Onset.....	Sudden and overwhelming	Gradual, hours or even days
Pain.....	Severe, often pleuritic; no typical localization	Pressing or crushing; substernal to shoulder and arm
Dyspnea.....	May be sudden and intense; at times, suffocating	Generally mild; when severe, intensity mounts gradually
Cyanosis.....	May be marked; not relieved by O ₂	Usually mild, or not at all
Shock.....	Frequently a first symptom; may precede pain in one-third of patients	When present, it is a culmination of several hours of increasing pain
Syncope.....	May be initial symptom	Rare; may be terminal symptom
Pulse.....	At onset, rapid and thready	At onset, normal or even slow
Blood pressure.....	Generally low (part of shock)	At onset, may be normal or even high
Fever.....	Early; may reach high levels	Twenty-four to thirty-six hours after onset; moderate
Leukocytosis.....	Early; high count	Second or third day; moderate increase
Icteric index.....	Often increased (hepatic anoxemia?)	Not altered
X-ray.....	Pulmonary infarction? Dilated pulmonary artery?	Not characteristic Pulmonary congestion?
ECG.....	Early pattern: atypical right bundle branch block Later pattern: large S ₁ , Q ₃ and negative T ₃	Early pattern: RST rise in leads II and III Later pattern: Q ₂ , Q ₃ and negative T ₂ and T ₃

number of graphs have clearcut features of the pattern described for acute cor pulmonale. Furthermore, even when the pattern lacks convincing features, it differs sufficiently from those seen in acute coronary thrombosis to aid in ruling out the latter condition. For electrocardiographic changes in coronary thrombosis with posterior wall infarction, especially during its early transient stage, are convincing. They are characterized by broad, elevated RST segments and conspicuous Q waves in leads II and III. Corresponding RST depressions may appear in lead I and in chest leads. The T waves in leads II and III are inverted to a varying degree. In the chest leads the T waves are always upright. (Fig. 5.) This early pattern is distinctive and there is little

the two conditions are, as a rule, strikingly different. It is the partial restitution pattern during a clinically quiescent stage of coronary thrombosis which the electrocardiographic pattern of an acute cor pulmonale may, at times, resemble, but in these cases, too, there are several basic differences in their respective graphs. After the initial RST changes in coronary thrombosis have disappeared, the restitution or "steady" pattern retains a Q₂, a Q₃ and a deeply inverted T₃. As a rule, T₂ follows in pattern and is usually also inverted or partly inverted for weeks or months. In the electrocardiogram of an acute cor pulmonale as a result of pulmonary embolization, a large Q₃ and a negative T₃ are conspicuous features. However, lead II is not similarly

affected. A well defined Q wave and a negative T wave in lead II are exceptional. Furthermore, a deep S wave in lead I, never present in coronary thrombosis, is a prominent component of the cor pulmonale pattern. In contrasting the two graphs in question one is impressed by the fact that in coronary thrombosis with posterior wall infarction, lead II is a miniature of lead III and that in acute cor pulmonale lead II bears a resemblance to lead I.

In conclusion, one is impelled to reemphasize that electrocardiograms, or for that matter any other single diagnostic aid, should never be permitted to dominate one's judgment in diagnosis. It is the sum total of all facts elicited from the history, physical findings, laboratory and graphic studies that finally determine the diagnosis. It is with this in mind that a differential diagnostic table (Table I) is appended. Within it are tabulated in parallel columns such significant facts in the history and clinical and graphic findings as may, by virtue of some of their striking contrasts, help in the differential diagnosis between acute pulmonary embolization and an acute coronary thrombosis with posterior wall infarction.

SUMMARY

1. Massive pulmonary embolization is a dramatic clinical syndrome of equal interest to physicians and surgeons. Autopsy records disclose that a large number of cases escape detection and clinical experience teaches that among those diagnosed the mortality rate is unusually high.

2. Diagnostic problems are many and are due mainly to the fact that acute pulmonary embolization often simulates other acute clinical syndromes.

3. While pulmonary embolization is more frequently encountered on medical services where a large number of chronic cardiacs

are treated, its incidence among surgical patients is equally important. It is among these that early recognition and timely treatment of pulmonary embolization directly determine prognosis.

4. The differential diagnosis between acute pulmonary embolization and coronary thrombosis with posterior wall infarction, being perhaps the most common problem, is discussed in considerable detail, with special attention to electrocardiographic features. A differential diagnostic table is appended.

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3 East 69th Street.

Origin of Thirst in Diabetes Insipidus*†

JOSEPH H. HOLMES, M.D. and MAGNUS I. GREGERSEN, M.D.

New York, New York

DIABETES insipidus, as an outstanding example of polydipsia, offers an opportunity to correlate this extreme type of thirst with our studies on normal man and dog.^{2,5,14,24,25} Whether thirst in this disease is primary or whether it is secondary to the polyuria has been discussed for many years. Bellows and Van Wagenen,¹ from a review of the literature and from the results of their own experiments on hypophysectomized dogs with esophageal fistulas, suggest that the polydipsia is the primary functional disturbance.

Yet the successful control of the polyuria and polydipsia of diabetes insipidus by the antidiuretic hormone of the posterior pituitary gland indicates that the polydipsia is secondary to the polyuria. If this is true, the bodily changes in diabetes insipidus should be those of a mild dehydration, the result of the excessive urinary excretion of water. The mechanism of the thirst should then be similar to that observed in dehydration. If this reasoning is correct, untreated diabetes insipidus should be associated with a decrease in plasma volume, extracellular fluid volume and salivary flow similar to that observed in water deprivation.^{2,3,4,34,35,36} The alleviation of the thirst by pitressin therapy** should produce increases in plasma volume, extracellular fluid volume and salivary flow similar to that observed when water is ingested by dehydrated individuals.^{2,5,34,35,36} Furthermore, the giving of fluids more rapidly than they can be eliminated by the kidney

should alleviate the thirst as effectively as pituitrin therapy.

The present studies were undertaken to determine whether: (1) the fluid changes in untreated diabetes insipidus are comparable to those of mild dehydration, (2) the alleviation of thirst by adequate doses of pituitrin alters these changes in the direction of normal hydration, (3) without medication thirst can be alleviated by giving fluid more rapidly than it can be excreted and (4) ingestion of salt induces a thirst response similar to that observed in normal man.

PROCEDURE

Observations were made on five cases of diabetes insipidus. The patients were studied under the following situations:

Period I. Control period: fluids *ad libitum*.

Period II. Pituitrin therapy: during this period the patients received 1 ampule of pitressin (20 pressor units) subcutaneously every six hours.

Period III. Forcing of fluids: water and liquids were forced until thirst was absent and salivary flow approached the values observed during the period of pitressin therapy.

Period IV. High salt intake: the patient was allowed fluids as desired and given daily 11.0 Gm. of NaCl and 3 Gm. of sodium bicarbonate divided into five equal doses and administered at four-hour intervals from 6 A.M. to 10 P.M.

Each period was of three or four days' duration. The measurements of plasma volume and available fluid were always made on the morning of the third day. Determinations of the hematocrit value and

**The pitressin used in these experiments was furnished us through the courtesy of Parke, Davis & Company.

*From the Department of Physiology of the College of Physicians and Surgeons, Columbia University, New York, N. Y.

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of the concentrations of serum protein, sodium and chloride were made at the time of the plasma volume measurement and also on two earlier occasions during each period of study. However, as the experiments progressed it was impossible to ob-

output. Body weight was observed four times daily and more often during periods of rapid shift. The patients were given a standard hospital diet of constant caloric intake and were permitted to add salt to the diet as desired. The amount used was re-

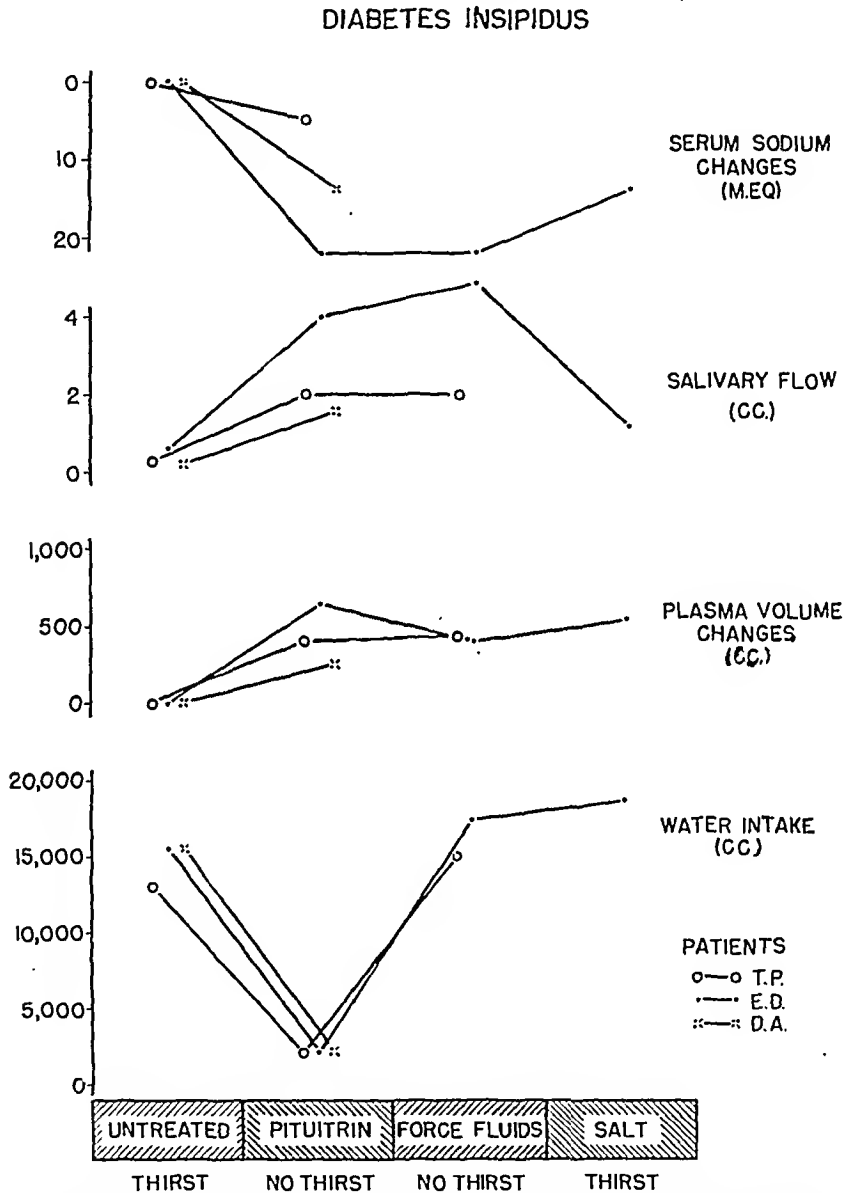


FIG. 1. The effect of various regimens (pitressin therapy, high fluid intake and high salt intake) on serum sodium salivary flow, plasma volume and fluid intake in patients with diabetes insipidus.

tain cooperation in every instance so that plasma volume and available fluid measurements were completed in only three patients and salt administered to only one.

During each period twenty-four-hour records were kept of fluid intake and urinary

output. Body weight was observed four times daily and more often during periods of rapid shift. The patients were given a standard hospital diet of constant caloric intake and were permitted to add salt to the diet as desired. The amount used was re-

corded and this figure together with the computed salt content of the diet gave an approximation of the sodium chloride intake.

The salivary flow was measured during a five-minute period of mouth breathing.²

These measurements were made at approximately 9 and 11 A.M. and at 2, 4 and 8 P.M. It was found that there were minor fluctuations in salivary flow throughout the day but that tests taken at the same hour on successive days of the same regimen were remarkably constant.

Following the technic of Gregersen and Stewart,⁶ simultaneous measurements were made of the plasma volume by the dye dilution method (T-1824) and of the extracellular volume by the thiocyanate method.⁷ All blood samples were taken from the antecubital vein and during the period of sampling the water intake was maintained at the same level as during the previous twenty-four hours. Other blood analyses included determination of the hematocrit value by the Wintrobe tube, of the serum protein by the falling drop⁸ or refractometric methods,⁹ of the serum chloride¹⁰ and of the serum sodium.¹¹ Urine samples were analyzed for chloride^{12,39} and sodium.¹¹

RESULTS

Figure 1 illustrates the significant changes observed in three cases studied. Without treatment the patients complained continually of thirst, fluid intake was high and there was a significant reduction in salivary flow. Adequate pitressin therapy not only alleviated the thirst but reduced water intake and urinary output to normal values.¹⁴ There were increases in weight, plasma volume and salivary flow.

When pitressin therapy was started on E. D., the body weight increased 3 Kg. within eight hours. There was an immediate reduction in urinary excretion but it was not until four to six hours after starting pitressin that the excessive thirst disappeared and water intake dropped to normal levels. The increase in salivary flow occurred at the time the thirst was alleviated but there was no evidence that the pitressin injections had any specific effect on salivary flow. Peters¹³ has reported similar increases in weight after starting pitressin therapy in patients with diabetes insipidus.

The increased salivary flow, plasma

volume and body weight observed during pitressin therapy were practically duplicated by simply forcing fluids to the point when thirst disappeared. The intake exceeded the output. The retention of fluid was comparable to that observed during

TABLE I
OBSERVATIONS IN CASE E. D.

	Period I (Control)	Period II (Pitressin)	Period III (Forced Fluid)	Period IV (Salt)
Water intake (L.)		3 1	17 3	18 7
Urine output (L.)	15 6	2 6	15 6	17 7
Weight (Kg.)	60 8	62 0	62 7	62 3
Salivary flow (cc /5 min.)	0 6	4 0	4 9	1 2
Plasma volume (cc.)	2,440 0	3,070 0	2,800 0	2,980 0
"Available fluid" (L.)	13 8	14 8	16 8	16 9
Serum proteins (Gm. %)	7 5	6 8	6 2	5 7
Serum sodium (mEq./L.)	155 0	133 7	133 1	141 7
Urine NaCl (Gm./24 hr.)*	9 5	11 1	6 4	23 2

* Represent average for each four-day period

pitressin therapy. The patient, E. D., testified that the forcing of fluid dispelled the thirst as effectively as did pitressin therapy. Furthermore, his appetite was improved and he lost the lethargic feeling of which he complained during the control period.

The beneficial effects of the forcing of fluids are further confirmed by the fact that E. D. voluntarily followed a regimen of this type after stopping pitressin therapy because of the inconvenience of administering subcutaneous injections. On awakening in the morning he is very thirsty and during the next thirty minutes drinks 2 to 3 liters of fluid. He repeats this procedure several times during the day. As a result his thirst is alleviated and salivary flow increases. While E. D. was on this regimen, observations were made several times of the changes in salivary flow, the body weight, the concentrations of serum sodium and serum proteins and the hematocrit value. The results of one day's observations are presented in Table II. In the morning, before taking water, his weight was 65.5 Kg. Two hours after drinking water his weight was 68.3 Kg. and remained at this higher level until bedtime. The reduction in concentration of serum proteins and serum sodium represent a 5 to 10 per cent increase in plasma and

extracellular fluid volume respectively. A comparison of Table II with Figure 1 shows that E. D. repeats every day the situations existing in periods I and III. These changes are consistent with those observed when a

TABLE II

CHANGES IN WEIGHT, SALIVARY FLOW, SERUM PROTEINS AND SERUM SODIUM WHEN THE PATIENT (E. D.) WAS IN A DEHYDRATED STATE ON ARISING IN THE MORNING AND AFTER THE THIRST WAS ABOLISHED BY INGESTION OF 3 LITERS OF WATER

	Weight Kg.	Salivary Flow cc./5 min.	Plasma Proteins Gm. %	Serum Na+ mEq./L.	Thirst
A.M. before drinking	65.5	0.1	7.75	146	Marked
2 hr. after water (3 L.)	67.3	2.0	7.1	138	None
5 P.M.	67.6	2.8	6.9	138.8	None, slight

normal dehydrated person restores his water deficit.^{2,36}

In the case of E. D. salt was given as a means of increasing the plasma and extracellular volumes to values comparable with those observed during the periods of pitressin therapy or when fluids were forced. The giving of salt caused intense thirst and a reduction of salivary flow similar to that seen during the control period. There was an increase in water intake and urine output similar to that reported by other investigators.^{13,15,16,17} After an initial period of salt retention urinary excretion of chloride equalled the NaCl intake. The serum sodium concentration fluctuated between 141 and 145 Meq. per liter. (Table I.)

The changes in salivary flow for the five cases are tabulated in Table III. These measurements were made at the time of the blood volume studies and show that the salivary flow was consistently reduced in untreated diabetes insipidus at a time when the thirst was intense. During the periods of pitressin therapy and the forcing of fluids thirst was alleviated and the salivary flow rose. For comparison five normal subjects were tested for a two to three-week period and the values for salivary flow in the normal subject were found to be similar to those in the patients only during the

periods of pitressin therapy or of the forcing of fluids. In two of these subjects the forcing of fluids up to 12 to 16 liters per day did not produce any increase in salivary flow.

The values for serum sodium concentra-

TABLE III

CHANGES IN SALIVARY FLOW (EXPRESSED AS CC. PER FIVE-MINUTE PERIOD) IN FIVE CASES OF DIABETES INSIPIDUS. THIRST WAS SEVERE IN PERIODS I AND IV AND ABSENT IN PERIODS II AND III

Patient	Period I (Un- treated)	Period II (Pitressin)	Period III (Forced Fluids)	Period IV (Salt)
	cc./5 min.	cc./5 min.	cc./5 min.	cc./5 min.
E. D.	0.6	4.0	4.9	1.2
T. P.	0.3	2.0	2.0	
S. D.	0.2	2.6	1.0	
L.	0.2	2.8	1.2	
D. A.	0.2	1.6		

tion are presented in Table IV. These were determined on blood samples taken at the time the plasma volume measurements were made. Many other sodium determinations were done in these patients and served to amplify and support the results shown in Table IV. The highest serum sodium values are noted in Period I (water *ad libitum*) and in the case of E. D. are well above normal values for man.³² In every instance there was a drop in concentration of serum sodium both during the period of pitressin therapy (Period II) and when fluids were forced (Period III). Serum chlorides were done in three patients and the changes observed were similar to those noted for serum sodium.

When values for the extracellular volumes were calculated from the variations in concentration of serum sodium or chloride, the changes were always in the same direction but occasionally not as large as the corresponding change measured by the thio-cyanate. Although it was not possible to carry out accurate balance studies in these patients, it is presumed that this difference could be accounted for by urinary excretion of sodium and chloride. The extracellular volumes observed for E. D. shown in Table I

were higher in the periods of pitressin therapy (II) and of the forcing of fluids (III) than in the control period (I). Similar changes were noted in the other patients.

Determinations of plasma protein concentration and hematocrit values were made

TABLE IV

VALUES FOR SERUM SODIUM IN FIVE CASES OF DIABETES INSIPIDUS SHOWING THE CHANGES WHICH OCCUR WITH PITRESSIN THERAPY, FORCING OF FLUIDS OR ADMINISTRATION OF SALT

Patient	Period I (Un- treated)	Period II (Pitressin)	Period III (Forced Fluids)	Period IV (Salt)
	mEq./L.	mEq./L.	mEq./L.	mEq./L.
E. D.	155	133.7	133.1	141.7
T. P.	142.5	137.2		
S. D.	143	137	136	
L.	146.5	141.3	141.0	
D. A.*	137.2	123.6		

* This patient also had adrenal insufficiency which accounts for the low values of serum sodium.

frequently in these patients to obtain additional information on the plasma volume changes. It can be seen in Table V that the serum protein concentrations were high during untreated diabetes insipidus and decreased when the fluids were forced or pitressin therapy was given. In untreated diabetes insipidus patients there were considerable fluctuations in the values, related apparently to temporary changes in water balance.*

* Dr. J. I. Nurnberger of the Neurological Institute, College of Physicians and Surgeons, Columbia University, observed recently in another case of diabetes insipidus the changes in fluid balance produced by pituitary injections. We made measurements of salivary flow in this same patient. Unfortunately, these measurements were not made on the same period of pituitrin therapy, but since the weight changes indicated approximately the same degree of hydration the data have been combined for comparison with the other five patients. Following pituitrin, the patient gained 3.2 Kg., the plasma volume increased from 2,640 to 2,940 cc., the plasma protein decreased from 7.2 to 5.6 Gm. per cent and the hematocrit value from 50.6 to 44.9. The salivary flow increased from 0.2 to 2.0 cc. per five-minute period. The injection completely alleviated the thirst and the urinary output dropped from approximately 6,000 to 900 cc. a day. The measurements in this patient confirm our earlier observations.

COMMENTS

The experimental evidence in the five cases of diabetes insipidus studied appears to support our hypothesis that the thirst and fluid changes in untreated diabetes insipidus are similar to those of mild dehy-

TABLE V

VALUES FOR PLASMA PROTEINS IN FIVE CASES OF DIABETES INSIPIDUS SHOWING THE CHANGES WHICH OCCUR WITH PITRESSIN THERAPY, FORCING OF FLUIDS OR ADMINISTRATION OF SALT

Patient	Period I (Un- treated)	Period II (Pitressin)	Period III (Forced Fluids)	Period IV (Salt)
	Gm. %	Gm. %	Gm. %	Gm. %
E. D.	7.5	6.5	6.2	5.7
T. P.	6.8	6.0	5.6	
S. D.	8.2	7.7	7.6	
L.	7.6	6.8	7.0	
D. A.	5.9	5.5		

dration. It was shown, furthermore, that pitressin therapy or the forcing of sufficient fluids to relieve thirst produces changes similar to those observed when water was given to normal dehydrated subjects.^{2,36} During these periods there were increases in salivary flow, in body weight, in plasma and extracellular volumes and decreases in hematocrit values and in concentrations of serum proteins, sodium and chloride. These changes are identical with those observed in dehydrated dogs⁵ or men after ingestion of water.^{2,34,35,36} Pitressin does not appear to exert any specific effect other than through its antidiuretic action since the same changes can be produced by the forcing of fluids. Salivary flow and thirst in diabetes insipidus can therefore be explained by Cannon's theory of thirst.^{14,37}

Gregersen^{14,38} suggests that the mechanism of the decrease in salivary flow in dehydration can be explained by a reduction in blood flow to the glands, and he demonstrated parallel reductions in salivary flow and plasma volume in dehydration produced by water deprivation and sweating. Parallel reductions in plasma volume and salivary flow were likewise found in our

patients in the untreated state when compared with the situation existing after pitressin therapy or the forcing of fluids. Furthermore, the presence in these patients of normal values for salivary flow only during the periods of pitressin therapy or forcing of fluids, and the observation that in normal hydration the forcing of fluids does not increase salivary flow suggest that the thirst mechanism and salivary flow changes of untreated diabetes insipidus are identical with those in dehydration.

There is evidence in the literature to support these observations. Findley and White²³ likewise found that thirst was alleviated in a case of diabetes insipidus in which fluids were forced to increase the polyuria. Also the observations by others on the effects of pitressin therapy on plasma volume^{18,19} and on serum concentrations of protein,¹³ sodium and chloride^{13,20} are similar to those shown in Tables I, IV and V. That the thirst of diabetes insipidus is a result of polyuria was shown in experiments on rats by Richter and Eckert²⁶ and by Swann.²⁷ These authors found that when the polyuria was controlled by ligation of the ureters thirst was absent. Furthermore, water deprivation in diabetes insipidus produces more marked signs of dehydration after twenty-four to forty-eight hours^{21,22} than are observed in the normal animal after eleven days of water deprivation.¹⁴

Other investigators have observed that the administration of salt in diabetes insipidus intensifies the thirst and increases the polyuria.^{13,15,16} When salt was given to E. D., the increase in plasma and extracellular volumes (NaSCN) were similar to or greater than those observed with pitressin therapy or the forcing of fluids. The thirst exhibited by E. D. following salt was also found in normal men when salt was administered by mouth or by intravenous injection of hypertonic salt solution.^{24,33} Normal men likewise exhibited an increase above the normal in plasma and extracellular volume and a decrease in salivary flow. This suggests that the thirst mechanism in diabetes insipidus responds in a normal

manner to the ingestion of salt. However, the magnitude of the thirst response provoked by ingestion of salt is much greater than in the normal because of the dehydration. This is in keeping with our observations that in the dog the giving of hypertonic salt solution in dehydration will evoke a much greater drinking response than would have been predicted from the sum of the drinking responses previously observed in either situation alone.⁵

At the high rate of fluid exchange that exists in diabetes insipidus frequent shifts in the fluid balance apparently occur. This is indicated by the marked variations in serum concentration of protein, sodium and chloride both in the untreated state or when starting pitressin therapy. If the patient abstains from drinking for a few hours, there will be a marked increase in concentration of serum sodium, chloride and proteins. In the case of D. A. after five hours of water deprivation the body weight decreased 4 per cent and at this time the serum protein concentration had increased 8.6 per cent, the serum sodium 8 per cent and the serum chloride 9.7 per cent. Similar changes in concentrations of serum sodium, chloride and protein have been reported by other investigators¹³ and some have even attached diagnostic significance to the variations.²⁸ Our measurements of plasma volume and extracellular volume reveal that the changes in serum concentrations of protein, sodium and chloride are in a large part merely a reflection of the changes in volume of the fluid compartments.

In the case of E. D. there appeared to be a slight increase in total twenty-four-hour chloride excretion when he was given pitressin therapy and a decrease when fluids were forced. (Table I.) However, the serum sodium changes showed a marked variation from patient to patient (Table V) and when correlated with extracellular volume changes (NaSCN) suggested a considerable variation in sodium and chloride excretion in the several test periods. This is in agreement with reports from the literature which indicate that in diabetes insipidus following

administration of pituitrin the urinary excretion of chloride may either increase,²⁹ decrease²⁰ or remain unchanged.³¹

CONCLUSIONS

Five cases of diabetes insipidus were studied to evaluate the mechanism of the polydipsia under the following situations: (1) water *ad libitum*, (2) pitressin therapy, (3) the forcing of fluids and (4) ingestion of salt (one case).

During the periods of intense thirst there was always a reduction of salivary flow. When thirst was abolished by pitressin therapy or by the forcing of fluids, the salivary flow increased to normal values. (Table III). These observations are consistent with the "dry mouth" theory of thirst.

Pitressin therapy or the forcing of fluids resulted in an increase in plasma volume and extracellular volume (NaSCN) over the values observed for untreated diabetes insipidus. (Fig. 1, Table I.) There were corresponding reductions in serum concentrations of protein, sodium and chloride. (Table IV and V).

It is suggested that the thirst mechanism in diabetes insipidus is similar to that observed in simple dehydration and is caused, in this instance, by the severe polyuria. This is confirmed by our observations that pitressin therapy or the forcing of fluids alleviate thirst and produce increases in plasma and extracellular volume and in salivary flow similar to that observed after ingestion of water in dehydration.

It is pointed out that the wide fluctuations of serum protein, sodium and chloride concentration are probably a reflection of marked variations in fluid balance. This is supported by simultaneous measurements of plasma and extracellular volume.

Salt, while it may be effective in maintaining plasma volume and available fluid (NaSCN) at the same levels as observed under pitressin therapy and when fluids are forced, does not abolish the thirst of diabetes insipidus, on the contrary, it increases the polydipsia. (Table I.) This reaction to salt

is the same as that seen in the normal person.

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Radiation Injuries of the Intestines*

CHARLES W. HOCK, M.D., JOSE RODRIGUES, M.D., ANNA HAMANN, M.D.†
and WALTER LINCOLN PALMER, M.D.

Chicago, Illinois

THE purpose of this paper is to discuss radiation injury of the intestine as seen in a series of patients treated for extrarectal pelvic cancer. Gastrointestinal symptoms from radiation were first described by Walsh in 1897; since then numerous reports of lesions so produced have appeared. The increasing use of radiation in the treatment of pelvic cancer, particularly cervical cancer, necessitates a careful study of the incidental injury of the intestinal tract.

In 344 diagnoses of carcinoma of the female reproductive system made by the gynecologic staff of the University Clinics the known incidence of injury of the intestine from irradiation is as follows:

State of the Carcinoma	No. of Cases	Intestinal Injuries	Percentage
Cervix	170	16	9.4
Uterus	101	3	2.9
Ovary	61	0	0.0
Vagina	2	0	0.0
Vulva	10	0	0.0
Total	344	19	5.5

Four of these patients received radiation therapy elsewhere and came to the University Clinics primarily for treatment of complications. In several additional patients the presence of carcinoma immediately adjacent to the site of irradiation made it impossible to evaluate the degree of radiation injury, if any; these have not been

included. The nineteen cases are summarized in Table 1.

Mild or acute reactions occur in half to two-thirds of the patients treated by combined x-ray and radium irradiation. An erythema in the rectum or bladder is frequently produced by the dosage required to cure the carcinoma. The reaction may be slight and pass unnoticed, but fairly frequently it is severe. It is evidenced by a burning sensation in the pelvis and by frequency of urination and of defecation. The condition usually clears up within ten days or two weeks, but in severe cases, from four to six weeks may be required. It is in this latter group as Jones^{11,12} noted that late rectal and bladder complications may develop, usually six or eight months after the initial irradiation. Acute reactions frequently occur also during the beginning of the third week of external irradiation by x-ray. The mildest symptoms are a slight diarrhea, two to four stools daily, without abdominal pain. In some instances, the symptoms are more severe, six to eight stools daily accompanied by colic-like pain. The diarrhea may be severe and profuse; the stools may be watery or mucoid, sometimes containing blood; nausea and vomiting may occur. These acute phenomena usually clear up completely after the irradiation is stopped. They may subside for a while to be followed sooner or later by a recurrence.

* From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

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The diagnosis in the acute reactions is easily established. Sigmoidoscopy discloses a diffuse hyperemia of the rectal mucosa, more marked on the anterior wall. The mucosa bleeds easily when touched. The

fatal reactions described by Todd,¹⁴ Mulligan,¹³ Cosbie⁵ and Cathie⁴ (1938) have been observed. Our interest has centered in the chronic ulceration, inflammation and fibrosis occurring as later manifestations and

TABLE I

Case	Age	Site of Tumor	Irradiation Technic
I	59	Corpus	1. Radium—4,800 mgh. (intra-uterine tandem only) 2. X-ray—11,000 r/air (5 portals)
II	55	Corpus	1. Radium—5,600 mgh. (intra-uterine tandem only) 2. X-ray—10,500 r/air (6 portals)
III	32	Cervix	1. Radium—4,900 mgh. (intra-uterine tandem plus 5 needles) 2. X-ray—10,500 r/air (6 portals)
IV	47	Cervix	1. X-ray—10,500 r/air (6 portals) 2. Radium—5,600 mgh. (intra-uterine tandem plus 5 needles)
V	51	Cervix	1. X-ray—10,500 r/air (6 portals) 2. Radium—4,800 mgh. (intra-uterine tandem plus 5 needles)
VI	70	Cervix	1. Radium—4,320 mgh. (2 capsules in crater) 2. X-ray—7,100 r/air (6 portals)
VII	31	Cervix	Irradiation done elsewhere, Radium X-ray
VIII	62	Cervix	1. Radium—3,650 mgh. (intra-cervical tandem only) 2. X-ray—9,600 r/air (5 portals)
IX	42	Cervix	1. Radium—?(4 applications in 15 months. Last application 12 needles) 2. X-ray—9,600 r/air (6 portals)
X	59	Cervix	Irradiation done elsewhere, Radium X-ray
XI	47	Cervix	Irradiation done elsewhere, Radium X-ray
XII	48	Corpus	X-ray (after hysterectomy) 5,000 r/air (6 large portals)
XIII	49	Cervix	1. Radium—4,800 mgh. (intra-uterine tandem plus 5 needles) 2. X-ray—9,600 r/air (6 portals)
XIV	52	Cervix	Irradiation done elsewhere, Radium X-ray
XV	59	Corpus	Irradiation done elsewhere, Radium X-ray
XVI	53	Cervix	Irradiation done elsewhere, Radium
XVII	39	Cervix	No specific information on dosage in history, Radium X-ray
XVIII	63	Cervix	1. X-ray—8,900 r/air (5 portals) 2. Radium—3,800 mgh. (intra-cervical tandem plus 3 needles)
XIX	34	Cervix	Irradiation done elsewhere, X-ray Radium

* Radium was given first followed by x-ray.

NOTE—All the cases were diagnosed by biopsy or dilatation and curettage.

area involved is variable in size, but usually it extends from about two inches above the anus to the rectopelvic juncture. A small ulcer surrounded by hyperemia may occasionally be found on the anterior wall of the rectum.

Mild early reactions such as these have not been included in our study because they are so common. None of the severe early

often difficult to distinguish from neoplastic invasion.^{2,3,5,6,8,10,14}

The symptoms of such lesions may appear at any time from shortly after the completion of irradiation to within several months or years later. They consist of abdominal pain, frequent bowel movements, tenesmus and the passage of varying amounts of blood and mucus by rectum. In some cases,

the initial symptoms are those of incomplete intestinal obstruction, i.e., cramp-like abdominal pain, vomiting and obstipation alternating with diarrhea. These may be due to a temporary obstruction caused by

On rectal examination proctitis and ulceration is felt as a slight irregularity at the level of the cervix with thickening of the mucosa. In perirectal fibrosis there is marked fixation of the entire rectum thus

TABLE I (Continued)

Approximate Tissue Doses in Rectosigmoid Region		Gastrointestinal Symptoms	
10,000–30,000 r in 2 days	41 days .	Diarrhea, obstipation	
3,000– 4,600 r in 37 days			
12,000–24,000 r in 2 days	38 days	Diarrhea, constipation, bloody stools	
2,100– 3,100 r in 31 days			
10,000–25,000 r in 2 days	44 days	Abdominal cramps, rectal bleeding, diarrhea	
3,200– 4,700 r in 39 days			
3,600– 6,000 r in 31 days	33 days	Progressive constipation	
12,000–30,000 r in 2 days			
2,400– 3,800 r in 34 days	112 days	Diarrhea	
10,000–25,000 r in 2 days			
15,000–22,000 r in 2 days	40 days . .	Vomiting, diarrhea, intestinal obstruction	
2,000– 3,000 r in 37 days			
Not estimated		Constipation, nausea, vomiting	
8,000–24,000 r in 3 days	48 days	Bloody diarrhea	
2,800– 4,200 r in 43 days			
? 15 months	2 years	Abdominal distress	
2,800– 3,600 r in 29 days			
2,200– 6,000 r in 24 days . . .		Diarrhea, abdominal pain, bloody stools	
10,000–25,000 r in 2 days	68 days	Nausea, bloody diarrhea	
2,400– 3,350 r in 65 days		Bloody stools, diarrhea, alternately constipation	
		Diarrhea	
		Diarrhea, intestinal obstruction	
		Vomiting, abdominal pain	
		(Terminal case)	
		Rectal bleeding, abdominal pain	
		Diarrhea, bloody stools	
		Diarrhea, bloody stools	
		Outcome	
I Ulceration stenosis		Died; colostomy, infiltration of tumor	
II Stenosis .		Resection of sigmoid stricture	
III Proctitis .		Incomplete obstruction sigmoid (10 months)	
IV Stenosis .		Resection of sigmoid stricture	
V Stenosis .		Extension of tumor?	
VI Stenosis . .		Resection of ileal strictures	
VII Ulceration .		Died; extension of tumor; x-ray fistula	
VIII Ulceration . .		Ulceration spontaneously improved	
IX Stenosis, telangiectases		Carcinoma progressed	
X Stenosis .		Carcinoma progressed	
XI Stenosis		Incomplete obstruction sigmoid	
XII Stenosis		Incomplete obstruction sigmoid	
XIII Stenosis .		Incomplete obstruction sigmoid, metastases	
XIV Stenosis . . .		Suicide; stenosis sigmoid	
XV Ulceration .		Died; peritonitis, perforation ulcer	
XVI Ulceration		Died; widespread metastases	
XVII Massive necrosis colon		Colostomy; peritonitis; died; necrosis colon	
XVIII Proctitis .		Spontaneous improvement	
XIX Ulceration .		Died; infiltration of tumor	

hyperemia, edema and spasm of the bowel at the site of the injury or to permanent obstruction caused by a true organic stricture.

increasing the confusion with an extensive carcinoma. In some instances, a very narrow stricture may prevent the passage of the finger. Occasionally, it is impossible to

reach the lesion with the finger and even proctosigmoidoscopy may not be decisive. The examination is usually very painful.

On sigmoidoscopy the typical ulcer, usually situated on the anterior rectal wall, is greyish white in color with an exudate of blood and pus in the base and surrounded by telangiectases. In perirectal fibrosis occlusion of the rectal lumen occurs more frequently; there may be no ulceration.

Roentgen studies are advisable when proctoscopy does not reach the lesion or when endoscopy is impossible. Barium enema or barium and air double contrast studies are much more satisfactory than the barium meal. The characteristic roentgenologic picture is illustrated in Figures 2 to 5.

Biopsy is somewhat hazardous because of the danger of perforation and fistula formation. If biopsy is desired, more than one piece of tissue should be taken from different places around the edge of the ulcer.

The decisive diagnosis between malignancy and irradiative injury may finally be made only by the improvement in general health following adequate treatment, relief of the intestinal symptoms and roentgen evidence of increasing size of the lumen of the bowel. In others the diagnosis may be confirmed only after resection of the process sometimes months after colostomy has been performed for the relief of acute symptoms.

Pathologically in the acute mild reactions, there is inflammation with edema of the mucosa with or without fibrinous deposits over the surface and with or without ulceration.⁷ The chronic lesions consist principally of inflammation with ulceration and sclerosis or combinations of the two; fistulas and strictures are frequent.¹⁵ The ulcerations range from irregular superficial areas of desquamation to deep, punched out ulcers. Telangiectases occur at the edges of the ulcerations. Stenosis is due to diffuse sclerosis with general constriction or to a

stricture at the site of ulceration. Histologically, edema is seen early together with progressive hyaline thickening in all layers of the wall and also in the vessels. Thrombosis and vascular sclerosis are prominent. The mucosa is focally destroyed. Degeneration and atrophy of the muscular coats may be present together with edema and vacuolization. The combination of atrophic fibers, swollen fibers and hyaline interstitial fibrosis is very striking. Figures 6 to 8 illustrate various phases of the reaction.

It is difficult in these injuries to evaluate the respective rôles of roentgen and radium irradiation; the former are probably responsible for the widespread lesions and the latter for those localized to the immediate neighborhood of cervix, uterus and vagina. In most cases, a summation effect is present. The radiotherapist is today equipped with rather detailed information on the quantitative distribution of radiation under variable conditions. This enables him to correlate treatment and reaction more exactly than was possible a decade ago. Both types of irradiation are better tolerated by the normal tissues if given at low intensities over longer periods than as massive doses in short times. In spite of the fractionation of x-rays, single doses can be high enough to cause vascular damage. A moderate figure of roentgen units can mean an overdosage if it is given together with a large amount of radium in a short time. The distribution of radium also plays an important rôle, for if it is placed improperly damage may occur even though the dosage and time intervals are correct. These problems of radiologic technic are mentioned to illustrate the importance of a well trained radiologist for the scrupulous planning of the combined treatment and also for the help he may be able to give in the differentiation of radiation sequelae and progressive cancer by means of information obtained from the details of dosage and technic.

It is possible that certain conditions may predispose to radiation injury of the intestine. Jones¹² suggested that pelvic inflammatory disease might fix the bowel in the pelvis and thus increase the exposure. Such a theory may explain the lesion found in the ileum in Case vi. This patient had pyometra associated with carcinoma of the cervix.

Aldridge¹ suggested that the accidental dislodgement of radium applicators from the cervical canal or uterine cavity to the vagina, retroversion of the uterus and the presence of peritoneal adhesions, fixing one or more loops of the intestine to the external surface of the uterus or to the cervical stump, might result in an excessive exposure. There is some evidence that diabetes and hyperthyroidism render the bowel more susceptible. It seems apparent, however, that frank overdosage is the most important factor. The individual variations in radio sensitivity are probably of minor importance. A dose well tolerated by the average patient should not cause severe irreversible and irreparable damage in any patient.

TREATMENT

In the treatment of the acute reactions, symptomatic medical treatment is usually satisfactory. Rest in bed, a bland diet, rectal instillations of warm oil, antispasmodics and sedatives are helpful. The more severe cases should be treated very carefully; dehydration and metabolic changes must be combated by means of parenteral fluids, saline, glucose and protein as indicated. Direct treatment of the rectal lesion by means of rectal irrigations with saline or weak antiseptics is probably of little value. The local application of radon-impregnated vaseline introduced by Whemann in 1928 might be beneficial if a satisfactory mode of application could be devised.

Surgery may be required because of stenosis, bleeding or pain. A colostomy is

imperative when the stenosis is marked. With incomplete obstruction due primarily to edema, conservative management may afford relief. Recurrent bleeding is occasionally severe enough to require colostomy. Persistent severe pain is at times a most difficult manifestation and may be relieved by presacral sympathectomy. In some cases both colostomy and presacral sympathectomy may be required. Resection of the inflamed portion of bowel is seldom necessary for healing usually occurs eventually. With resolution of the lesion, the stenosis lessens. Fistulas should be closed surgically unless they heal spontaneously in a reasonable time.

Wigby (1943) reports six colostomies in his series and Todd (1938) seven, all with excellent results. Bacon (1937) performed eight colostomies in fourteen patients with strictures.

In treatment, a great deal of attention must be given to the psychosomatic factors. Cancer-phobia is almost always present and necessitates a careful explanation of the nature of the condition. The diet will be varied according to the predominance of either constipation or diarrhea. Phenobarbital and belladonna are of some value.

Our experience may be best presented perhaps by a summary of the material and by descriptions of each case:

CASE REPORTS

CASE I. M. V., age fifty-nine, (245770) a diabetic with carcinoma of the corpus uteri, in July, 1944, received 4800 mgh. of radium (50 mg. for 96 hr.; 1 capsule 2 cm. in length). The x-ray treatment consisted of 10×300 r. including backscatter to each of four pelvic portals plus 5×300 r including backscatter to one perineal portal, from July 31, 1944 to August 28, 1944. Severe diarrhea appeared two months after the treatment followed a month later by constipation and partial intestinal obstruction. A colostomy was performed January 5, 1945. Proctoscopy some days later revealed a

sloughing ulcer in the rectum with marked edema of the rectal walls. A complete hysterectomy with bilateral salpingo-oophorectomy in July, 1945, disclosed malignant tissue in the uterus. Death occurred in February, 1946, after a febrile terminal course. At autopsy a fibrous stricture of the rectum 1.5 cm. in diameter, located 8 cm. above the anus was found. Metastatic carcinoma was present in the vagina.

Comment. This is an instance of frank radiation ulcer and stenosis of rectum. It also illustrates the problem of the proper distribution of radium because 4800 mgh. are usually tolerated if the radium is spread out over an area of 8 to 12 cm.² in the uterus rather than contained in a capsule only 2 cm.² The diabetes may have decreased the resistance to irradiation and to superimposed infection.

CASE II. F. B., fifty-five years of age, (264391) with carcinoma of the corpus uteri, received 5,600 mgh. of radium (100 mg. in fifty-six hours) in two capsules with a total length of 4 cm. on July 23, 1941. From August to September 2, 1941, she received x-ray treatments (10×300 r to four anterior and posterior pelvic portals and 4×300 r to two lateral pelvic portals), a total depth dose of 2,100 r to each parametrium and a possible maximum dose to the rectosigmoid of 3,400 r being delivered. About six months after the end of the treatment diarrhea developed alternating with constipation and accompanied by bloody stools. Symptoms of intestinal obstruction were present one month later. X-ray in March, 1942, showed marked obstruction of the lower sigmoid. At abdominal operation in March, 1942, no cancer was seen but there were adhesions of the sigmoid to the corpus uteri and a large patch of necrotic tissue was found in the sigmoid. A complete hysterectomy with bilateral salpingo-oophorectomy was performed. No cancer was found histologically. Resection of the sigmoid was performed six months later; no cancer was present, only "an area of constriction with fibrosis of the muscularis 3 cm. wide." In 1943, the patient was reported in good condition.

Comment. In this instance of stenosis of the sigmoid in an obese woman the post-radiation changes were well localized and again apparently resulted from the intensive local radium effect.

CASE III. M. V., thirty-two years of age, (154145) was discovered in the fifth week after delivery, to have cancer of the cervix. A capsule of 50 mg. of radium and 5 capsules of 10 mg. each were placed in the posterior lips of the cervix only, for forty-nine hours on January 14, 1943. On January 19, 1943, x-ray treatment was started: 10×220 r/eff. to two anterior and two posterior pelvic portals and 4×220 r/eff. to two lateral portals, instead of the perineum, because of the postpartum state and the local radium. The patient had diarrhea during the treatment, stopping at the end and recurring after one week for a few days. About four months after the end of treatment the patient complained of abdominal cramps, rectal bleeding and severe diarrhea. Proctoscopy at that time, August, 1943, showed an edematous, easily bleeding mucosa. X-ray in November, 1944, revealed "narrowing at the rectosigmoid junction not producing obstruction." (Fig. 1.)

Pelvic examination in November, 1944, at the time of the patient's last visit disclosed no evidence of recurrent carcinoma. The vault was clean; the cervix was not seen; the corpus could not be felt. A rectal structure was felt at the tip of the examining fingers; the walls of the rectum were firm, fixed and indurated.

Comment. The proctitis was attributed to local injury of the anterior rectosigmoid wall from the radiation in the immediately adjacent posterior lip of the cervix. The radium dosage was very considerable and it was localized; the roentgen irradiation in itself was not excessive but it was superimposed on the radium.

CASE IV. (Fig. 2.) G. H., thirty-seven years of age, (264832), with cancer of the cervix in stages III and IV extending into the vaginal wall, diagnosed in June, 1941, received roentgen irradiation 10×220 r/eff. to two anterior plus two posterior pelvic portals plus 4×220 r/eff.

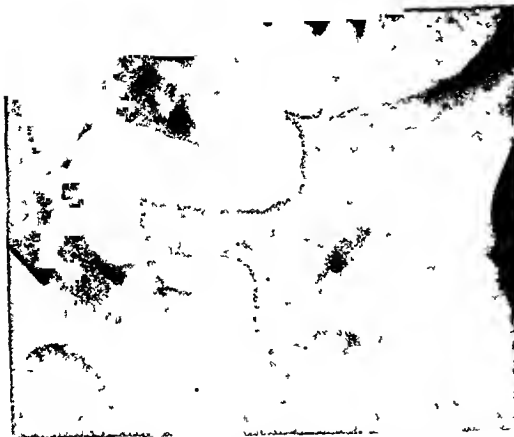


FIG. 1. Case III. Smooth stenotic deformity of the rectosigmoid twenty-two months after irradiation of the cervix uteri.



FIG. 2. Case IV. Stricture of the rectosigmoid subsequently resected and shown to be benign.

to two lateral pelvic portals, in thirty-one days, from June 26th to July 26th, 1941; radium was used in September 9 to 11, 1941, 1 capsule of 50 mg. and 5 of 10 mg. for fifty-six hours, a total of 5,600 mgh. Severe and progressive constipation appeared two months later necessitating colostomy in January, 1942. In May, 1943, a stricture at the rectosigmoid junction was resected. No histologic evidence of carcinoma was found in the resected bowel.

Comment. This is an instance of post-irradiation intestinal stricture in advanced cervical carcinoma involving the vagina. Interstitial radium seemed indicated in higher than routine dosage because of the extent of the tumor and even though the rather thin patient had already received a relatively high dosage of roentgen irradiation.

CASE V. I. W., fifty-one years of age, (271594), with carcinoma of the cervix, stages III and IV received $10 \times 220\text{r/air}$ to each of two anterior plus two posterior pelvic portals and $4 \times 220\text{r/air}$ to two lateral pelvic portals in thirty-four days from October 3, 1941, to November 5, 1941. Radium was given on January 20, 1942, 100 mg. for forty-eight hours, a total of 4,800 mgh. Diarrhea was present in April, 1942, but improved in June. In November, the patient complained of backache and vaginal discharge. X-ray in January, 1943, showed "narrowing at the rectosigmoid junction." In February, 1943, there was induration and fixation of the wall of the rectum. In

December, 1943, there was no evidence of vaginal recurrence but rectal examination revealed the entire pelvis to be filled with a firm mass. The rectum admitted only one finger. The patient has not been seen since that time.

Comment. The case is included in the present series because of the rather typical symptoms and roentgenologic manifestations. The pelvic tumor, however, seems surely attributable to uncontrolled, progressive carcinoma. The absence of cervical recurrence is rather common in the pelvic progression of cancer.

CASE VI. L. H., seventy years of age, (156236), with carcinoma of the cervix and pyometra (incision and drainage) together with stenosis of the vagina received radium treatment on August 11 to 13, 1936, 2 capsules for forty hours, 4,320 mgh. X-ray therapy was given from August 14 to September 19, 1936, $4 \times 300\text{r/air}$ to each of six portals.

Epigastric pain and vomiting were present in November, 1936. From 1937 to December, 1940, she developed recurring attacks of diarrhea with frequent attacks of upper abdominal pain and accompanied by hyperchromic anemia. Intestinal obstruction developed in December, 1940. X-ray examination disclosed obstruction of the ileum. At operation 50 cm. of ileum were resected because of an annular constriction at two points of the ileum together with an enterolith 4 by $2\frac{1}{2}$ cm. There was no evidence of cancer. (Fig. 3.)

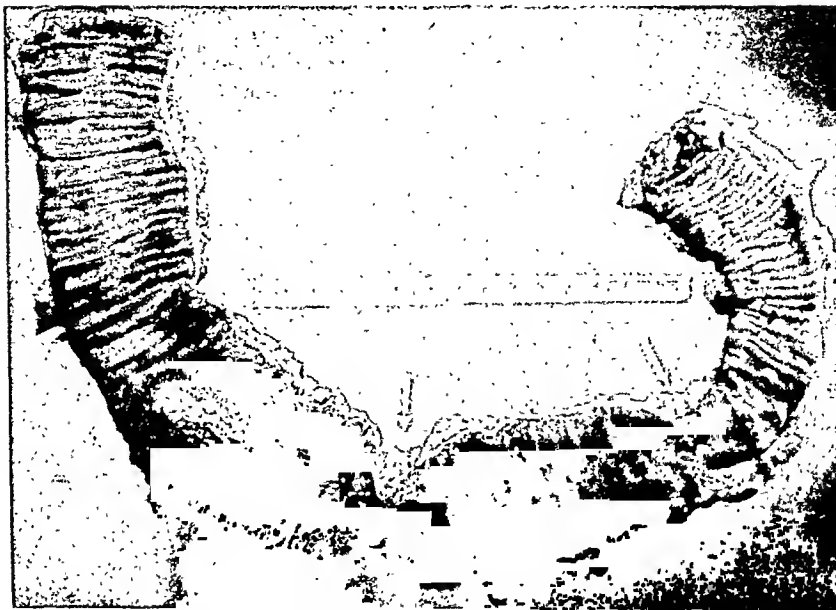


FIG. 3. Case VI. Postirradiation strictures of the ileum with a ball-valve enterolith.

Comment. This is an instance of post-irradiation stenosis of the ileum. Fixation of the ileum in the pelvis after inflammatory disease (pyometra) may have predisposed the bowel to injury. The dose of radium was not excessive, but it was given with high intensity; the placement was possibly not well controlled because of a narrow vagina. The x-ray therapy was administered more rapidly than is customary at present.

CASE VII. B. O., thirty-one years of age, (19007) a diabetic with septate vagina, was found to have carcinoma of two cervical stumps in 1930. In 1920, she had undergone a hysterectomy with left salpingo-oophorectomy for fibroid degeneration of the uterus. Five years earlier the right tube and ovary had been removed. Before the first operation the patient had pelvic gonorrhea. On February 14, 1930, she received radium implantation: 1 capsule of 50 mg. for twenty-five hours-2,500 mgh. in each orifice. The following x-ray treatments were given:

1. 550 r/air to ant. and post.
pelvis on Feb. 19-24, 1930
2. 628 r/air to ant. and post.
pelvis on May 19-20, 1930
3. 628 r/air to ant. and post.
pelvis on July 19-25, 1930

4. 628 r/air to ant. and post.
pelvis on Oct. 8-22, 1930
5. 472 r/air to ant. and post.
pelvis on Dec. 15-22, 1930

2906 r/air

in 10 months
(two portals only)

After the first x-ray treatment she was seen in the gastrointestinal clinic with general abdominal complaints: constipation, nausea and vomiting. On April 28, 1930, at proctoscopy, "there was some diffuse pallor of the mucous membrane, but no evidence of cancer." X-ray of the colon in May, 1930, was normal. The patient died on April 3, 1931. Autopsy revealed cancer in the vagina, posterior wall of the bladder and the anterior wall of the rectum. About 2.5 cm. above the anal orifice an opening of the rectum was observed into a larger cavity occupying most of the pelvic region. There was fibrous induration of the pelvic connective tissue with obstruction of the sigmoid colon. Histologically, the colonic mucosa appeared somewhat atrophic; the submucosa was fibrotic and infiltrated with round cells.

Comment. This is an instance of progressive cancer in scarred pelvic tissues. The radium irradiations were given only to a small area which may therefore have re-

covered relatively well in spite of the high dosage. The case is included as an instance of irradiation injury because of the typical location of the lesion in the rectum and the fibrosis noted in the submucosa of the rectosigmoid. As so often happens, it is difficult completely to separate the rôles played by the radiation and the neoplastic invasion.

CASE VIII. C. T., sixty-two years of age, (92722), with cancer of the cervix, underwent a vaginal operation for cystocele in April, 1943. Previously she had had an appendectomy, salpingectomy and excision of a fistula in ano. Radium was inserted on April 29, 1943, 1 capsule of 50 mg. for seventy-two hours—3600 mgh. in a surface of 2 cm. Beginning May 4, 1943, x-ray irradiation was instituted 10×300 r/eff. to two anterior and two posterior pelvic portals and 4×300 r/eff. to two lateral pelvic portals in forty-two days. (See data in summary for total dosage.) On February 8, 1944, the patient complained of bloody diarrhea with cramps. X-ray examination disclosed no obstruction but there was a suspicion of an ulcer fleck on the anterior rectal wall. The patient gradually improved and in May, 1945, was feeling much better with diarrhea occurring only occasionally.

Comment. This is interpreted as an ulcer of the anterior rectal wall due to the localized high dosage of radium and the superimposed roentgen irradiation.

CASE IX. A. F., forty-two years of age (150540), received an unknown amount of radium therapy elsewhere for cancer of the cervix on two occasions. About six months after the last treatment (September, 1935) abdominal distress appeared with some blood in the stools and low back pain. In May, 1936, a nodular tender mass in the left parametrium was found. It was thought to be adherent but not definitely fixed to the cervical stump! A diagnosis of recurrent carcinoma with extension to the left parametrium was made. X-ray treatment was started in May, 1936, $9 \times 200 \times 6$ pelvic portals. (See data in summary for total dosage.) At proctoscopy there was narrowing with painful spasm at 15 cm. with no ulceration,

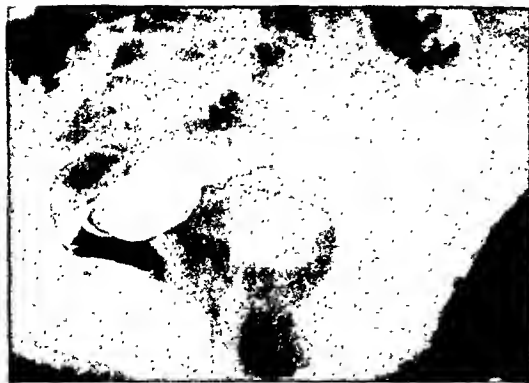
but a few tiny blood clots were adherent to the rectal wall.

Comment. Progressive cancer was evidently present in the left parametrium. The proctoscopic findings are suggestive of radiation injury, but complete differentiation in this instance is not possible.

CASE X. L. R., fifty-nine years of age (240852), had had a diagnosis of carcinoma of the cervix grade II made at another hospital for which she received a total dose of 6,000 mg. hours of radium in April, 1940. From May 3 to June 11, 1940, she received 10×220 r/air to each of four pelvic portals and 4×220 r/air to a perineal portal for a total tissue dose of 3,120 r in the parametrium. In November, 1940, she began to have diarrhea associated with cramp-like lower abdominal pain and blood in the stools. X-ray and proctoscopic examinations revealed a narrowing of the colon for a distance of 8 cm. beginning 15 to 18 cm. above the anus. She complained of blood in the stools intermittently the next three years. In April, 1944, she was hospitalized because of weakness, pain in the left upper extremity and shoulder and tenderness over the left costal margin. X-ray of the chest revealed bilateral pulmonary metastases. The patient died in September, 1944, in another hospital.

Comment. The patient evidently died from metastatic carcinoma of the cervix. The diagnosis of post-irradiation sigmoiditis is based upon the bloody diarrhea appearing seven months after a large dose of radium and also upon the roentgenologic appearance of the sigmoid. (Fig. 4.)

CASE XI. M. G., forty-seven years of age (253635), was treated for cancer of the cervix by radium and x-ray at another hospital in April, 1940. The patient experienced nausea and diarrhea with mucus and blood during the irradiation. In November, 1940, a small amount of red blood appeared in the stools. Proctoscopy on December 6, 1940, revealed "an area of fibrosis at 10 and 14 cm. Free blood was present, coming from beyond the fibrosis." X-ray examination on December 7, 1940, disclosed a



4

FIG. 4. Case x. Moderate deformity of the sigmoid eight months after irradiation.



5

FIG. 5. Case xii. Stricture of the rectosigmoid six months after hysterectomy and roentgen irradiation of the pelvis for carcinoma of the corpus uteri.

peculiar narrowing of the rectosigmoid confirmed at another examination December 11, 1940. On February 18, 1941, the patient wrote that the bleeding from the rectum was very little but she did not return to the clinic.

Comment. The diagnosis in this case also is based on the appearance of bloody diarrhea after irradiation of a cancer of the cervix together with the proctoscopic and roentgenologic findings. A biopsy of the rectal stricture was negative for carcinoma.

CASE XII. (Fig. 5.) J. M., forty-eight years of age (273559), had an incomplete hysterectomy and bilateral salpingo-oophorectomy in June, 1941, at another hospital for cancer of the corpus uteri. X-ray therapy was given after the operation (5900 r depth in six portals). In December, 1941, she passed some blood per rectum. A mass was felt in the left cul-de-sac. Proctoscopy on January 3, 1942, was considered normal. At another proctoscopy on January 9, 1942, the mucosa was described as mildly edematous. Difficulty was encountered in passing the instrument beyond 10 cm. On May 21, 1942, at the third proctoscopy the mucosa was described as bleeding more easily than normal and the same difficulty in passing the instrument beyond 10 cm. On May 21, 1942, at the third proctoscopy the mucosa was described as bleeding more easily than normal and the same difficulty in passing the instrument was encountered. A proctoscopic biopsy disclosed no evidence of carcinoma.

Diarrhea was still present alternating with

constipation. X-ray examination of the colon in January and again in June, 1942, disclosed a narrowing of about 8 cm. of the rectosigmoid interpreted as probable post-irradiation change. (Fig. 5.) The patient was not seen again.

Comment. This patient received no radium and the dosage of roentgen irradiation was not unusual. However, the roentgenologic and proctoscopic findings were considered more characteristic of radiation injury than of neoplastic invasion. Conclusive evidence, however, is not available.

CASE XIII. M. S., forty-nine years of age (199025), with cancer of the cervix graded III and IV had had an appendectomy and oophorectomy in 1914. Radium was inserted on June 7, 1938 (100 mg. for forty-seven hours-4700 mgh., interstitial method). X-ray therapy was given 9×300 r/eff. to two anterior and two posterior pelvic portals and 7×300 r/eff. to two lateral portals, from June 10 to September 30, 1938. (See data in summary for total dosage.) Diarrhea appeared during treatment and lasted only a few weeks. In April, 1943, x-rays examination disclosed "narrowing of the rectosigmoid junction, probably due to fibrosis." The patient has not been seen since October, 1943, when she received x-ray therapy for metastases.

Comment. The diagnosis in this case is based upon the appearance of diarrhea during the roentgen irradiation and subsequent to the radium and also upon the

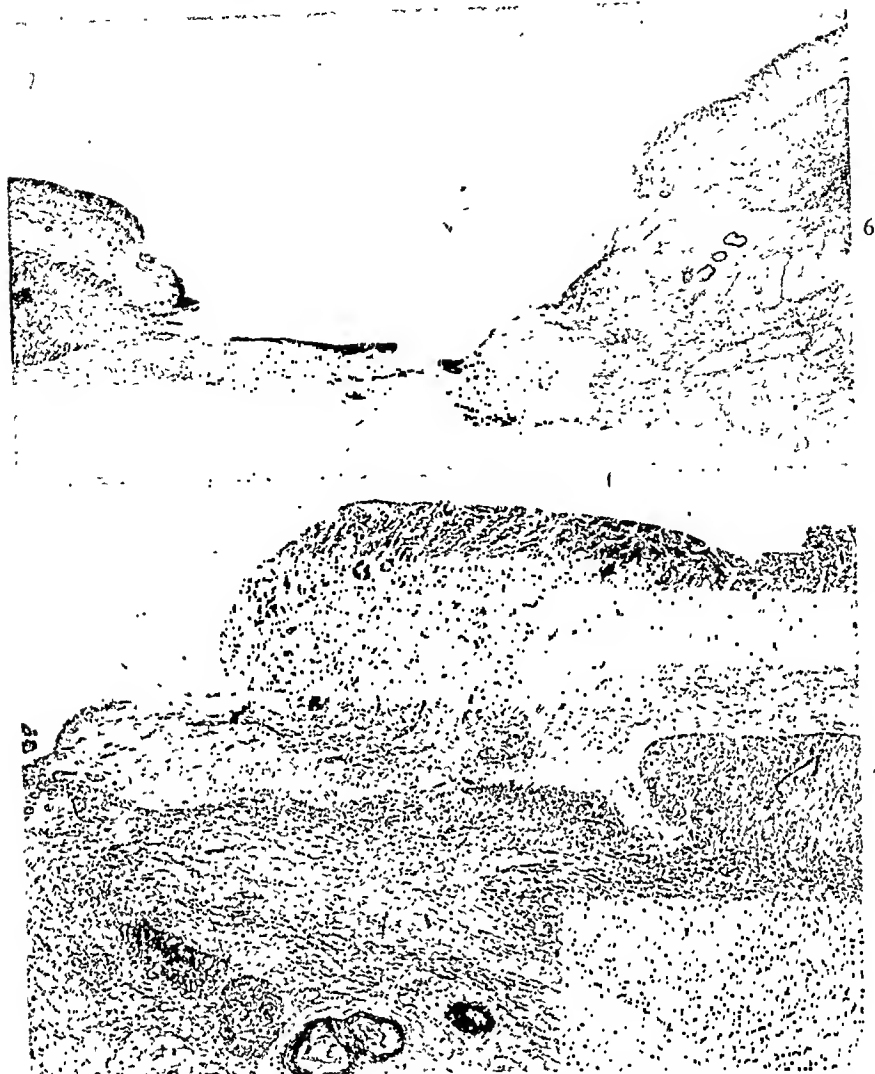


FIG. 6. Case xv. Deep chronic ulcer of the colon, with a perforation in its floor where scar tissue has replaced the muscle coats (hematoxylin and eosin, $\times 8$).
 FIG. 7. Case xv. Margin of ulcer illustrated in Figure 6, showing edema, fibroplasia and telangiectases in the submucosa; fibrous tissue replacing the muscle coats; thick-walled hyalinized arteries and thrombosed veins (hematoxylin and eosin, $\times 30$).

roentgenologic demonstration of narrowing of the rectosigmoid four and a half years later.

CASE XIV. C. A., fifty-two years of age (184320), with cancer of the cervix received radium treatment on September 30, 1937 (100 mg. for thirty-six hours-3600 mgh.). A febrile period followed. Roentgen irradiation was given 5×200 r/air to six pelvic portals from October 4, 1937, to October 23, 1937, and 3×200 -300 r/air to three pelvic portals from November 5, 1937, to November 26, 1937. Another radium treatment was given in Janu-

ary, 1938, (100 mg. $\times 24$ hours-2400 mgh). After two weeks of diarrhea, tenesmus and abdominal soreness the patient developed acute intestinal obstruction requiring a colostomy on March 16, 1938. X-ray examination March 14, 1936, had shown a "high grade obstruction to the passage of barium in the mid-sigmoid for 5-6 cm." A pelvic abscess was drained in April. In October the colostomy was closed.

On November 1, 1938, the patient leaped from a window of the hospital. Autopsy revealed apparent cure of the cancer, "status post-irradiation" with stenosis of the sigmoid and obstruction of the left ureter. Microscopic studies

showed hyalinized fibrous tissue with sclerotic vessels containing foci of round cells but no tumor.

Comment. The stenosis of the sigmoid seems definitely attributable to the radium and roentgen irradiation.

CASE XV. (Figs. 6 and 7.) M. F., fifty-nine years of age (221852), with adenocarcinoma of the uterus and diabetes mellitus received radium treatment June 17, 1939 (5000 mgh.) and the routine x-ray treatment (10×220 to two anterior and two posterior pelvic portals and 3×220 to two lateral pelvic portals) in about eighty days. Recurrence of the tumor was found and a second radium treatment was given on October 25, 1940 (100 mg. \times 36 hours-3600 mgh.). Another course of x-ray therapy was given in twenty days; ($3 \times 230 \times 7$ portals, October 1940). Cauterization of intracervical cancer with acetone was performed September 9, 1941 (recurrence).

On October 14, 1941, the patient developed vomiting, fever and severe abdominal pain. Death occurred on October 31, 1941. Autopsy revealed fibrinopurulent peritonitis, cancer of the uterus filled with necrotic masses; the rectum contained a sharply circumscribed deep ulcer 18 by 14 mm. in size and about 3 to 4 mm. deep. The floor of the ulcer was dark greenish-grey. Through a perforation in the floor of the ulcer a 2 mm. probe passed readily into the pouch of Douglas.

Comment. Progressive cancer, irradiation ulcer in the rectum and peritonitis presumably from perforation of the ulcer were present. With the large amount of necrotic tissue in the uterus the peritonitis may have been present before the perforation. The diabetes may have decreased the resistance to irradiation. The dose (x-ray and radium) surpassed the tolerance dose purposely in the palliative attempt to decrease the hemorrhage.

CASE XVI. M. B., fifty-three years of age (223852), was admitted for cancer of the cervix with lung and liver metastases too advanced for

further therapy. Four radium treatments, amount unknown, had been given elsewhere.

The patient died on August 8, 1939. Autopsy revealed cancer of the cervix with metastasis into the broad ligaments, pelvic lymphatic glands, lungs and liver. An ulcer was found on the rectal wall, behind the cervix, 3 cm. in diameter, round, penetrating the entire thickness of the rectal wall at its deepest point (radium ulcer).

Comment. This patient was apparently treated very inadequately, with radium only, causing local damage without reaching the distant points of the carcinoma. The symptoms due to radiation injury were not discernible clinically.

CASE XVII. (Fig. 8.) P. G., thirty-nine years of age (351346), received three radium and thirty-six x-ray treatments (dosages not available) for carcinoma of the cervix at another institution in 1940. Rectal pain started after x-ray therapy. Approximately four years after the last treatment, the patient noted bleeding from the rectum and the appearance of abdominal pain. Colostomy for the relief of the abdominal pain was performed in February, 1944. Exploration of the intestine and closure of the colostomy was carried out on February 12, 1945. Peritonitis developed ten days later; death occurred March 4, 1945. Necropsy revealed diffuse peritonitis and a massive necrosis of the colon a short distance above the site of repair of the colostomy. Sections taken from the region of the colostomy showed an increase in fibrosis with an occasional suture thread or pus pocket present. One small area consisted almost entirely of multinuclear giant cells. Sections from the stricture of the sigmoid 14 cm. above the anus showed edema with submucosal and adventitial fibrosis but with no evidence of carcinoma.

Comment. Overdosage not only locally but over a large area was apparently responsible for the extensive injury.

CASE XVIII. M. P., sixty-three years of age (306990), with a squamous cell carcinoma of the cervix received a total of 5,000 roentgen units



FIG. 8. Case xvii. Margin of an erosion illustrating the telangiectatic thin-walled blood vessels, the atrophic mucosa and the submucosal fibroplasia of chronic irradiation injury. (The superficial epithelium has sloughed post-mortem.) (Hematoxylin and eosin, $\times 110$.)

to the upper end of the vagina and pericervical region and 2800 r. units to the parametria at the wall of the pelvis between April 22, and September 11, 1943. In May the x-ray therapy had to be interrupted because of diarrhea. Radium treatment was given between June 10th and 12th for a total of 3,800 mgh.

The patient was seen October 16, 1944 at which time she complained that daily for a year she had had from one to three loose stools containing small amounts of bright red blood. Proctoscopy to 10 cm. showed a normal mucosa but some bloody mucus was present in the lumen. The rectosigmoid region was very active; the proctoscope could not be advanced further because of pain. Mild inflammatory changes were noted in the rectosigmoid on fluoroscopy. There has been no recurrence of symptoms.

Impression. Mild radiation injury lasting longer than usual but without demonstrable ulceration or marked stenosis.

CASE XIX. (Fig. 9.) R. S., thirty-four years of age (298154), with carcinoma of the cervix was given x-ray therapy but it had to be discontinued because of continued bleeding in spite of repeated transfusions of whole blood. Later

the x-ray therapy was resumed in the Out-Patient Department, the patient receiving between December 9, 1942, and January 23, 1943, a total of 4,300 r. to the cervix. She was given 3,400 mgh. of radium to the corpus, cervix and cervical canal. By November 12, 1943, she complained of a mass in the vagina with severe pelvic pain, diarrhea and bloody stools. By February 15, 1944, nausea, vomiting and abdominal distention were added to the previous complaints. The patient's final admission was on April 7, 1944. Opiates and cobra venom were given because of severe pain. Death occurred on April 12, 1944.

Autopsy revealed extensive ulceration and sloughing of most of the cervix; carcinomatous infiltration of the parametrium, vaginal wall, and urinary bladder; large vesico-vaginal fistula with complete destruction of the ureteral orifices and distal ends of the ureter; post-irradiation ulcers and atrophic-fibrotic changes in the colon just above the rectosigmoid junction; kinking of the colon and adhesive fixation to the uterine corpus in the ulcerated region.

Histologically, a section from the region of irradiation injury shows a flat sclerotic ulcer infiltrated by polymorphonuclear cells. There is increased connective tissue in the submucosa, in the serosa and in a dense fibrous adhesion.

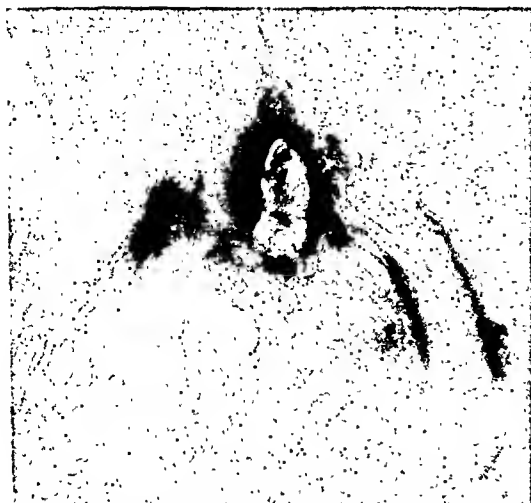


FIG. 9. Case XIX. Typical radiation ulcer showing marked telangiectases; autopsy specimen.

Comment. This patient with extensive inoperable cancer of the cervix received moderate amounts of radium and roentgen irradiation; at autopsy fifteen months later definite evidence of radiation injury of the bowel was present.

SUMMARY

The outstanding early symptom of radiation injury of the intestine is diarrhea, mild to severe in degree. Later manifestations are pain, demonstrable ulceration and stricture formation with partial or complete obstruction. The early lesions, located usually on the anterior wall of the rectum and rectosigmoid, are characterized by an edematous friable mucous membrane. Later ulceration, with a grayish white slough, occurs at the level of the cervix. In time perirectal fibrosis resembling a "frozen" pelvis may develop and result in obstruction. In the severe injuries with stenosis, hemorrhage or persistent severe pain, temporary or permanent colostomy may be required with or without resection of the bowel. Intractable pain may be treated by colostomy and resection of the afferent nerve supply to the rectum. The ideal therapy is, of course, prophylactic, the

avoidance of radiation injury. Whether or not it is possible by attention to the details of technic to administer effective carcinocidal doses of irradiation without occasional severe injury to adjacent normal tissue such as the rectum seems questionable at present.

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Lichen Planus, Atypical

A Report of Ten Cases

ARTHUR A. HOLBROOK, M.D.

Milwaukee, Wisconsin

LICHEN planus manifested itself among troops in the Southwest Pacific Area in a manner hitherto never observed. Army medical authority directed that the disease be labeled "lichen planus, atypical." When sufficient data have been accumulated and studied a more specific term will undoubtedly be assigned. On searching through four recent editions of standard textbooks only one description was found which seemed applicable to the cases herewith presented. The elder Sutton¹ wrote that he had seen two rare cases of lichen planus in which large, purplish papules with stellate bases had coalesced at various points to form a net-like arrangement. His diagnosis was "lichen planus hypertrophicus, retiformis." All but one of the patients in this series showed this same process which is called "reticulation" in Table 1. The exception, Case x, had far less active lesions than the others, the nodules lacking the finger-like offshoots upon which strand formation apparently depends.

CASE REPORTS

CASE I. A forty-two year old lineman entered the hospital on February 17, 1944, with a generalized eruption of a month's duration.

He had gone to New Guinea in July, 1943. In October he noticed small blisters on the inner sides of both wrists which itched intensely, especially at night. Since his work brought him into contact with all types of vegetation, a diagnosis of dermatitis venenata was made and calamine lotion was prescribed. The blisters soon dried up but the skin remained rough, red and irritated. Two months later groups of blisters

broke out on the inner aspects of both thighs. This eruption cleared entirely with the same lotion.

In January, 1944, the skin of the upper anterior chest grew rough with a myriad of tiny, pointed elevations each having a whitish core which could be expressed as a needle-like plug. This matter could easily be pulverized between the fingers and rubbing the roughened skin produced a powdery shower. A similar process soon developed over the neck, arms and legs and within a few days became generalized. Itching was the only distressing symptom.

Within a matter of days the "roughness wore off, leaving purplish spots which were raised." The latter tended to run together and grew scaly; thereupon, the itching ceased. About three weeks later he arrived at this hospital.

The family history was negative for skin disease and not remarkable for allergy. Several times before entering the Army the patient had had "poison ivy" which yielded promptly to treatment; otherwise, his skin had always been clear. He smoked about thirty cigarettes daily and drank six to eight cups of coffee. He had taken one atabrine tablet (0.1 Gm.) daily, six times a week for seven months.

The physical examination revealed a well developed but undernourished man in no distress. The scalp was hardened with tightly packed fine scales. A marked, patchy alopecia was present. The eyebrows had disappeared. The skin of the face as well as of the rest of the body was distorted by purplish, raised, irregular nodules 1 to 2 cm. in diameter. Coalescence had occurred to produce solid expanses over the forearms and thighs and net-like patterns over the trunk, arms and legs. The dorsal and lumbar spine areas were also involved, the extent of the lesions increasing from above, downward as far

as the belt line. Strands of reticulation sloped off to the sides giving the effect of a spruce tree pattern. The belt line was relatively free. There was fine sealing of all the lesions. Lichenification was marked about the neck, wrists and ankles. The palms and soles were undergoing patchy

adenopathy and pitting edema of the ankles was present. The only other significant finding was marked pyorrhea.

The results of laboratory examinations were as follows: the red blood cell count 3,910,000; the hemoglobin 80 per cent; the white blood

TABLE I

THE DISTRIBUTION OF THE SIGNIFICANT PHYSICAL FINDINGS IN THE TEN CASES OF LICHEN PLANUS

Lesions of the Skin	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII	Case VIII	Case IX	Case X
Physical Properties										
Polygonal papules.	+	++	+++	0	++	++	+	0	+	+
Acuminate papules.	+++	0	0	0	0	0	0	0	0	0
Umbilicated papules.	0	+	++	0	0	0	0	0	0	++
Nodules.	+++	+++	+++	+++	+++	+++	+	+++	+++	+++
Violet or purple.	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Wickham's striae.	+++	+++	+++	0	++	++	0	+++	0	0
Patterns										
Reticulation.	+++	+++	+++	+++	+++	+++	+++	+++	+++	0
Solid expanses.	+++	+++	+++	+++	+++	++	+++	++	+	0
Lichenification.	+++	+++	+++	+++	+++	++	+++	++	+++	0
Distribution										
Lines of cleavage.	+	+	++	+	+	+	+++	+	+	0
Flexor surfaces.	+	+	+	+	+	+	0	+	+++	0
Nerve distribution.	+	+	++	0	0	0	+++	0	0	0
Generalized.	+++	+++	+++	+++	0	0	+++	0	0	0
Special Sites										
Scalp.	+++	+++	++	+++	+++	++	+	+++	0	0
Eyelids.	+	+++	+++	+++	+++	+++	+++	+++	0	0
Palms.	++	++	0	0	++	++	++	+++	0	0
Fingernails.	+++	+++	0	0	0	+++	++	+++	0	0
Soles.	++	++	0	0	++	++	0	++	0	0
Toenails.	+++	+++	0	0	0	+++	0	0	0	0
Glans penis.	+	++	0	0	0	0	0	0	0	+
Lesions of the Mucous Membranes of the										
Mouth										
Buccal.	0	+++	0	0	++	0	0	++	++	0
Lingual.	0	0	0	0	++	0	0	+++	0	0
Labial.	0	+	+	++	+++	+	+++	++	++	++
Other Features										
Skin										
Exfoliation.	0	++	0	0	0	+++	++	+++	0	0
Secondary infection.	0	0	+++	0	0	0	++	0	0	0
Linear lesions.	0	0	0	0	0	0	0	0	+++	+
Bullous lesions.	0	0	+++	0	0	0	0	0	0	0
Miscellaneous										
Adenopathy.	++	+++	+++	+++	++	+++	+++	+++	+++	+++
Ankle edema.	++	+++	+++	+++	0	+	+++	+++	0	0

0 means Absent. + means Slight Degree. ++ means Moderate Degree. +++ means Marked Degree.

peeling. A number of the toe and fingernails were lifted by a subungual accumulation of hard granular material which was darkly pigmented. These nails were grooved and pitted. A single, annular, slightly raised violet lesion was found on the glans penis. There was generalized

cell count 7,050 with polymorphonuclears 73 per cent, lymphocytes 25 per cent and eosinophiles 2 per cent. The sedimentation rate was 9 mm. in one hour. A urinalysis, the Kahn test, an x-ray film of the chest and an electrocardiogram were all normal.

For medication the patient was given phenobarbital, ferrous sulfate and atabrine by mouth; an antipruritic lotion for general application and a sulfur salicylic acid ointment for the thickened areas of the skin as well as bismuth sub-salicylate in oil intramuscularly once a week. He was kept at rest much of the time and the use of tobacco and coffee was curtailed. Because of pyorrhea fifteen teeth were extracted and dental plates prepared.

The chart was normal throughout the patient's stay. New lesions appeared on the face, abdomen and feet as small violet nodules which grew larger and developed fine scales. The older purple lesions turned a greyish-brown color and in the course of three months flattened out. On April 8, 1944, two biopsies were performed. A week before evacuation the patient noticed that after bathing with soap and water his towel would grow dirtier the more he rubbed his skin. At the same time areas of light skin appeared where thickened and darkly pigmented expanses had existed. Needless to say, this turn in the course of events did a great deal to buoy the patient's spirits which had been periodically depressed. He left by plane for the United States on May 16, 1944.

*Pathological Report.** The specimen was taken from the anterior thigh and it contained a nodular, dark-purplish, slightly scaly lesion which was about two months old. Microscopically, there was moderate hyperkeratosis, hypertrophy of the epithelium and marked broadening and downgrowth of the rete pegs. The basement membrane appeared irregular because of thin streamers of cells which extended into the underlying corium. The latter was edematous and contained many new blood vessels, a heavy infiltration of lymphocytes and much coarse brown pigment.

The upper back was the site of this biopsy which included a patch of fine, papular lesions with central plugging and a dirty color. Microscopically, the epithelium was extensively pigmented. Its surface was irregular due to thickenings apparently associated with downgrowth of the rete pegs. Beneath these areas

the corium showed increased vascularity, a slight amount of round cell infiltration and pigmentation.

This patient had the most marked skin involvement of any in the series; nevertheless, the blood studies and his symptomatology were not remarkable.

CASE II. This thirty-three year old mechanic was admitted in March 17, 1944, because of a skin disorder which had involved his whole body for a period of a month.

On October 1, 1943, the patient arrived in New Guinea. About four months later (January 12, 1944), he developed a reddish, dry, scaling patch on the inner aspect of the right thigh just above the knee. One week later both palms began to peel and at the same time red and scaling spots appeared on various parts of his body. They became raised and turned purplish. The involvement was most marked at points of irritation like the belt, collar lines and the shoulder tops. Itching at night was intense. Blisters broke out on a number of the nodules. Within several weeks the rash had become widespread and dependent edema was first noted.

The family history was negative for skin diseases but positive for allergy, in that two cousins and one uncle had suffered from hay fever. In the past the patient had had a few minor fungous infections between the toes and once in the crotch, all of which responded quickly to treatment. Otherwise his skin had always been clear and his health excellent. He had taken one atabrine tablet (0.1 Gm.) daily for five and one-half months without any untoward effect.

Upon physical examination the patient was found to be well developed but quite thin. Despite his affliction he was cheerful. The scalp was practically identical with that of the previous patient. He also had nodular unit lesions which coalesced into broad expanses with lichenification and elsewhere into reticular configurations. These lesions were of a bright, reddish-purple color and associated with a generalized diffuse violaceous erythema. Scaling was prominent, the individual scales being shiny, white, thin and large. There was spotty des-

* All the pathological reports in this article were prepared by Lieut. Col. Edward A. Birge, Medical Corps, Army of the United States.

quamation of the palms and soles. The nails were affected as was described in case 1. The glans penis contained two nodules marked by fine whitish striae. The buccal mucous membrane showed both linear and annular, milky-white, raised lesions bilaterally. The annular ones were juxtaposed to large, gold, dental crowns. The lips presented a chapped appearance and areas of brown pigmentation not limited to the vermilion portion. The post-auricular, cervical, axillary, epitrochlear and inguinal glands were all enlarged but not tender. The lower edge of the liver was palpated two finger breadths below the costal margin. The ankles were markedly swollen with pitting edema.

The white blood cell count was 10,950 with polymorphonuclears 77 per cent and eosinophiles 6 per cent. The sedimentation rate was 11 mm. in one hour. Other routine tests were not remarkable. A serum protein determination as well as an x-ray film of the chest were both normal.

The patient was kept in bed and was given phenobarbital and bismuth subsalicylate in the buttocks at weekly intervals while mineral oil was administered to the skin. With rest in bed the edema gradually subsided but never disappeared. For about ten days he ran an afternoon fever as high as 102°F., without any symptoms other than feeling hot. There were no physical findings to explain the fever and the laboratory studies, including malaria smears, were negative. When the afternoon application of mineral oil to the whole body was stopped the fever promptly subsided. On April 14, 1944, two skin specimens were removed surgically. During the six week period of hospitalization there was no significant change in the dermatological condition. He departed for the United States on May 1, 1944.

Pathological Report. The specimen came from the anterior chest and represented a section of a strand in the so-called "reticular pattern." Clinically, the lesion was raised, reddish-purple and scaling. It was considered to be about two and one-half months old.

Microscopically, the epithelium was thin and edematous. Moderate hyperkeratosis was present. Little remained of the rete pegs except a

few thin columns of cells. The corium was vascularized and infiltrated by many lymphocytes and it revealed a moderate amount of fine brown pigment lying in macrophages. There was some inflammatory reaction around the hair shafts and sweat glands in the section. The lesion from the thigh had been present for about three months. It was nodular, raised, rough, and purple. The so-called "broad expanses" were made up of such units.

Microscopically, hyperkeratosis was marked. The epithelium was heaped into thin, irregular papillary folds giving the appearance of a verruca. There was an associated, irregular down-growth and broadening of the rete pegs. The papillae of the corium were edematous; they were also highly vascularized and infiltrated by numerous lymphocytes. A moderate amount of coarse, brown pigment lay free in the interstices of the corium as well as inside macrophages. A little of this pigment was seen in the epithelium.

This was the only patient with fever of obscure origin. The relationship between the fever and the general application of mineral oil appeared to have been satisfactorily established.

CASE III. A tank gunner, nineteen years of age, came into the hospital as a litter case on March 21, 1944, complaining of skin trouble lasting for five months and which had become generalized ten days before admission.

When eight years old the patient had scarlet fever and at that time white spots had developed on various parts of his body, including the eyelids, and had never disappeared. In October, 1943, the patient landed on Goodenough Island and subsequently went to Cape Gloucester on New Britain. After a few weeks of exposure to the tropical sun, the upper eyelids became sunburned and highly irritated. Similar white patches on his bare arms were next involved; finally, those on his trunk and legs also became red, dry, scaly and tender even though covered by clothing. Unlike an ordinary sunburn the condition did not clear. About January 15, 1944, oval and round spots of the same kind developed on the normal skin, especially on the legs. These areas were raised, "maroon" in

color and extremely itchy. He felt well and kept at his job.

Various lotions and ointments were prescribed at the dispensary but none proved effective; therefore, he was admitted to the nearest hospital and in the early part of March was given a series of epsom salt baths. After the third treatment, his "whole skin broke out" and he grew too sick to take much notice of the types of lesions. He was evacuated by plane.

No member of his family was known to have had skin or allergic diseases of any kind. Except for the vitiligo the patient had never had any skin disease nor had he ever suffered from hives, hay fever or asthma. He had taken atabrine daily for six months in 0.1 Gm. doses without difficulty.

On physical examination the patient appeared undernourished, acutely ill, weak and uncomfortable. The outstanding skin lesions were upon his chest, back and legs and were manifested by a dense, nodular eruption with coalescing ulcerations whose bases were covered with purulent discharge. Elsewhere, polygonal and umbilicated papules, nodules with striae and other features listed in Table I were present. The neck, antecubital and popliteal areas oozed moderately. Several bullae were found superimposed on nodular elements, one over a shoulder blade being about 1 inch long and sausage-shaped. The back showed a solid expanse of involvement with the spruce tree effect. The entire belt line was relatively free. There was a mild, patchy alopecia with slight scaling of the scalp. The vermilion portions of the lips contained pigmented spots. Verrucous plaques were prominent over the buttocks and thighs and the ankles were swollen with pitting edema.

The laboratory studies revealed: red blood cell count 4,960,000; hemoglobin 65 per cent; white blood cell count 14,050 with stabs 14 per cent, segments 70 per cent, lymphocytes 7 per cent, monocytes 3 per cent, eosinophiles 5 per cent and basophiles 1 per cent. The urinalysis and Kahn tests were negative. A sedimentation rate was 40 mm. in one hour.

Treatment consisted of bed rest, colloidal baths, boric acid compresses to the eyes and ears and alibour solution compresses to the ulcerated lesions followed by cod liver oil dress-

ings. The response was excellent. As the infected areas cleared within the first week, the fever which had persisted around 101°F., gradually subsided. On the twelfth day the sedimentation rate had fallen to 21 mm. per hour; thereupon, bismuth injections were started on a weekly basis. As the acute dermatitis subsided, the patches of vitiligo could be discerned over the eyelids, arms, trunk, genitalia and legs. They varied in diameter from 1 to 3 inches. The lichen planus reticular strands of nodules in these depigmented areas were the most distinctly violet colored of any in this series of cases. Whereas, those lesions in the adjoining normal skin assumed a darker purplish hue and later turned brownish. Biopsies were taken of the different types on April 8, 1944. At the time of transfer on April 28, 1944, considerable improvement was evident, especially about the eyes and over the trunk. The ankle edema had disappeared and the patient was well on his way to regaining the 36 pounds he had lost.

Pathological Report. This specimen was excised from the abdominal wall where reticulation involved both normal and depigmented skin. The lesion was violet, raised and finely scaling. It had been evolving for approximately two and one-half months.

Microscopically, there was moderate hyperkeratosis. The rete pegs showed an irregular broadening and downgrowth and a few small epithelial pearls were found in them. The epithelium between the pegs was thin and atrophic. At one place a tendency toward the formation of verrucous papillae was evident. The corium was infiltrated by large numbers of lymphocytes and a few eosinophiles. New blood vessels were also prominent, especially just beneath the epithelium and about the hair follicles; in addition, small amounts of brown pigment were present.

A skin nodule was excised from the anterior chest. This lesion was umbilicated, covered with fine scales and colored violet. In one segment it gave a pseudopod-like offshoot which was considered indicative of the manner in which reticulation is produced. The histologic picture was the same as described for the specimen obtained from the abdominal wall, except that the papillary downgrowth was more striking.

No histopathological difference was noted between the lichen planus lesions of the normal skin and those of the vitiligo patches.

CASE IV. A thirty year old, military policeman was admitted on April 25, 1944, because of generalized skin disease. He had been in New Guinea for eight months. Six months before admission he developed a vesicular rash on the volar aspect of both forearms which was attributed to a certain red sap from trees he had been handling in building a mess hall. Under treatment with merthiolate the eruption disappeared in six days.

Four months before admission the dorsa of his feet and toes began to itch. Calamine lotion afforded relief. Subsequently, the pruritus involved the rest of the legs and soon spread over his entire body. There was no rash. At the same time he developed three dime-sized sores on the lower lip which were painful, raw and oozing. Crusts formed, and the lip became swollen. After two months of various kinds of topical applications the lesions healed.

Approximately two months before admission his arms, legs and eyelids became sunburned. Contrary to previous experience the affected skin became unduly red and swollen. In ten days it began to scale. This process then extended over the whole body and became complicated by red blotches the size of dimes, quarters and half-dollars. These spots were raised over the dorsa of the arms and the itching became more intense and interfered with sleep. The blotches tended to coalesce and in the region of the knees they became covered with blisters. The latter broke and formed "sores with pus." Elsewhere, similar ulcerations developed as scaling occurred, being most marked over points of pressure such as the hips and elbows. The patient stated that scratching produced blisters the size and shape of his little finger. His ankles and lower legs became swollen.

During the month before coming to this hospital he was given various kinds of treatment, the most helpful of which was boric acid soaks. This promoted a "shedding of skin, scales and crusts," which left a bright red, clean delicate surface. The latter promptly "dried out, scaled up and formed small bumps."

The family and past histories were negative for allergic and skin diseases, except that the patient had had mild evidences of "athlete's foot" which always responded quickly to common disinfectants. In October, 1943, he suffered an attack of dysentery and in December an attack of malaria. The latter recurred about one month before admission. He had taken atabrine regularly as a suppressive measure and the same drug was used therapeutically on both occasions.

The patient was a well developed and well nourished soldier in no distress. He presented a widespread violaceous erythema, nodular reticulation with scaling and solid expanses of thickened, rough, plaque-like lesions with a greenish-grey surface. The latter were distributed over the lumbar and gluteal areas, the extensor aspects of the elbows and knees and over the ankles. There was pronounced, diffuse alopecia and loss of pubic hair. The eyelids were lichenified. The lips were diffusely pigmented and they showed lacy, bluish-white striae. The ventral part of the belt line was relatively uninvolved. Other positive and negative findings are indicated in Table 1.

The urine was normal and the Kahn tests were negative. The red blood cell count was 4,800,000 and the hemoglobin 14 Gm. The white blood cell count was 13,900 with 66 per cent polymorphonuclears and 15 per cent eosinophiles. The sedimentation rate was 11 mm. in one hour and the serum proteins totaled 5.2 Gm. per cent. The clinical chart was normal.

The patient was given a course of penicillin therapy: 20,000 units intramuscularly every three hours for eight and one-half days. No significant change of any kind was observed; therefore, the measure was abandoned and bismuth injections were begun. Local applications of mineral oil kept the skin pliable and seemed to cut down the tendency to scale. On May 9, 1944, a skin lesion was biopsied. When he departed for the United States on May 15, 1944, the eyelids had shown the most improvement. The nodular elements remained about the same throughout his stay in the hospital.

Pathological Report. The abdominal wall was the site of this biopsy. The skin in this region showed violaceous erythema, scaling and thickened strands arranged in net-like patterns.

Microscopically, the epithelium showed adjoining areas of hypertrophy and atrophy. In the latter, the epithelium was represented merely by a thickened layer of keratin and a few, very thin lines of basal cells. The hypertrophied portion revealed definite hyperkeratosis. The rete pegs were broad and thick and from them, thin streamers of cells stretched out into the corium. The corium was extensively vascularized and infiltrated by lymphocytes with an occasional eosinophile. The inflammatory process was restricted to the region immediately beneath the epithelium, although some extension was noted along a hair shaft which was included in the section. No increase in pigmentation was observed.

The course of penicillin therapy was tried empirically. Since the lesions of lichen planus were in no way changed, this medication was not used further.

CASE V. This twenty-five year old infantryman came into the hospital on March 31, 1944, complaining of a generalized skin disease which had started six weeks previous to admission.

In December, 1943, he had gone to New Guinea and after about one month he began feeling below par and started losing weight. In mid-February, 1944, red, itching blotches appeared on his palms and soles without any known provocation. Similar lesions soon developed on his arms and legs and spread rapidly over his whole body. The eyelids, nose and lips were early involved by inflammation and dryness accompanied by burning and itching. This was followed by oozing and crusting. He was first hospitalized on March 24th and was evacuated south by airplane.

The family history and the past personal history were negative for allergy and skin disease. He had taken atabrine regularly for four months without any difficulties. Physically the patient was poorly nourished and weak. His morale, however, was good. An outstanding feature was the marked degree of sanguineous crusting of the lips and nose; the latter was entirely and solidly encased in a dark-reddish, scab-like formation which was thick and closely adherent. The upper and lower eyelids were similarly affected although to a milder degree. The palms

and soles showed a patchy peeling and the limb and trunk lesions were lightly scaling. The other findings are scored in Table 1.

A complete blood count and urinalysis were normal. A Kahn test and a malaria smear were both negative. The chart was flat. The patient weighed about 120 pounds whereas his normal weight was 135 pounds. Treatment was primarily directed toward improving his general condition by diet and rest. Without sedation he slept most of the time during the first ten days. The crusts had to be soaked for five or six days before they loosened sufficiently to be removed. On April 8, 1944, two biopsies were done. Bismuth injections were begun before his departure on May 1, 1944.

Pathological Report. This specimen, which was removed from the right upper arm, consisted of a patch of discrete, violet papules with central plugging. The sections showed moderate hyperkeratosis and a tendency of the epithelium to form tiny, verrucous papillae. The rete pegs had enlarged in irregular fashion both downwards and to the sides. One small area of hemorrhage was found in the epithelium. The corium was filled with round cells and new capillaries to which was added a small amount of brown pigment.

The second preparation was a hypertrophic nodule with fine scaling and a violet color which had been developing for about six weeks on the volar aspect of the left forearm. The description for the first specimen applied to this specimen as well, except that the hypertrophy of the rete pegs in the second specimen was more marked and more brown pigment was present.

CASE VI. A forty-one year old orderly entered the hospital on February 7, 1944, with a generalized eruption of several weeks' duration.

He had arrived in New Guinea in August, 1943, feeling well; however, after a few weeks he lost his appetite for no known reason. By the first of January, 1944, his weight had dropped from 145 pounds to 130 pounds and he felt weak. About January 10, 1944, after using a broom in routine fashion, he developed a large blister on his right palm. This had never happened before. Within a day or two the dorsa of both hands grew red and scaly but not itchy. There had been

no known exposure to any irritant. The affected skin proceeded to peel. Potassium permanganate soaks were prescribed at the dispensary and used three times a day for three weeks. After the first few times the rawness and scaling extended up the arms and appeared on the legs and within a few days the whole body was involved and he became acutely ill.

The family history was non-contributory. Except for mild and intermittent "athlete's foot," the past history was negative for skin diseases. He had never had hay fever, hives or asthma. The daily taking of one atabrine tablet for six months before admission had never upset him.

The physical examination revealed a well developed but emaciated soldier who weighed about 105 pounds, whereas his normal weight was 160 pounds. The entire integument was scaling in large flakes and exhibited a diffuse violet erythema. Over the shins, upper trunk and arms were dark purple nodules which had coalesced into solid expanses as well as reticular patterns. A number of polygonal papules were found about the eyes and the fingernails and toenails were the most affected of any of the patients in the series. The majority had been so raised by pigmented material beneath the nails that as the matter crumbled away the nails themselves were left quite detached. Patchy alopecia and pigment changes in the lips were also noteworthy.

The most significant laboratory finding was a white blood cell count of 9,850, with 36 per cent eosinophiles. This was checked the next day at 11,300 and 24 per cent, respectively. The urine and Kahn tests were negative while an x-ray examination of the chest was normal. Low grade fever was present.

The patient was kept at absolute bed rest and was fed as much food as he could tolerate which was supplemented by polyvitamin capsules. Mineral oil proved the most satisfactory unction for the skin. Itching was of little consequence and on February 10, 1944, a skin biopsy was performed. Improvement was slow, desquamation continuing actively for nearly five weeks. The eosinophile count fell to normal limits. A sedimentation rate on March 18, 1944, was 12 mm. in one hour. Not until exfoliation had practically stopped did he begin to gain weight,

although his appetite had been excellent throughout his stay in the hospital. When evacuated on April 29, 1944, he weighed 125 pounds, his face was well cleared and the purple nodules were generally flatter and more discrete while those on the legs showed fine whitish stippling.

Pathological Report. The biopsy site was the right shin where a purple nodule was excised from a "solid expanse." According to the history the lesion was about three weeks old. The clinical picture was complicated by an associated exfoliative dermatitis.

On microscopic examination there was marked thickening of the epithelium and hyperkeratosis. The rete pegs extended broadly and deeply. Hyperpigmentation was noteworthy. A massive infiltration of lymphocytes involved the upper portion of the corium. No eosinophiles nor leukocytes were found; in general, the corium was well supplied with new blood vessels.

It is interesting, that despite the high level of eosinophiles in the blood, none was found in the inflammatory infiltration of the corium.

CASE VII. A thirty-seven year old able-bodied seaman entered the hospital on May 28, 1944, complaining of a rash which had appeared one month previous to admission.

The patient stated that at the age of fourteen he had had a spotty eruption over the neck, arms, buttocks and legs which was diagnosed by a skin specialist as lichen planus. Without any treatment that he could recall the condition cleared entirely in a matter of six or eight months.

During the following twenty-three years the patient suffered no skin disease whatever. Toward the end of January, 1944, his ship took him to the New Guinea area but despite the intense heat he felt very well. Since he wore only shorts and shoes a general coat of tan was soon acquired. Approximately two months before admission, however, an old scar on his left shin began to crack, scale and turn red. The spot quickly enlarged and a similar process started on the other leg. After several weeks both areas became infected; thereupon, sulfanilamide powder was applied daily.

One month prior to entry both palms and the sides and backs of most of his fingers became dry, cracked and rough with scales. Soon, tiny "pimples" appeared on the backs of the hands and spread up the arms and across the shoulders and neck. No further treatment was given before he was evacuated to this hospital.

The family history was non-contributory. The past history was noteworthy for revealing a duodenal ulcer which had been proven by x-ray examination four years previously. Meanwhile he had controlled his symptoms satisfactorily with amphojel. At certain times of the year he suffered mild attacks of hay fever, the cause of which was never determined. During his service in the islands he took atabrine regularly without experiencing difficulty. He had not handled possible irritants, as for example, gasoline or brush but he admitted having developed "athlete's foot" just before his present illness. He had had a "chest cold" for approximately a week's time.

The positive physical findings were limited to the skin and chest. A shallow ulcer measuring 2 by 2½ inches and showing signs of pyogenic infection was present over the left shin. There was a similar but smaller one on the right shin. A fine papulopustular eruption with inflammation extended over the arms, shoulders, neck and to a lesser degree the legs. The skin of the backs of the hands and of the neck was thickened and lichenified. The palms showed patchy peeling. There was mild scaling and cracking between several toes. Increased voice transmission was found anteriorly over the third right interspace.

The laboratory examination revealed a temperature of 102°F., pulse 88 and respirations 20, as well as a normal urine and negative Kahn tests. The red blood cell count was 4,520,000; hemoglobin 14 Gm.; the white blood cell count 11,300 with polymorphonuclears 76.5 per cent, lymphocytes 12 per cent, monocytes 6.5 per cent and eosinophiles 5 per cent. A sedimentation rate was 40 mm. in an hour. An x-ray film of the chest revealed signs of patchy pneumonia in both upper lobes.

With complete bed rest, symptomatic treatment and wet boric acid compresses to the ulcers the temperature returned to normal by

lysis within eight days. Repeated examinations of the sputum and gastric contents on direct smear after concentration as well as on culture were negative for acid-fast bacilli. A second strength tuberculin test was positive. During the first three weeks the chest signs and symptoms subsided, the sedimentation rate fell to 18 mm. and the white blood count fell to 7,750. The eosinophiles, however, rose to 12 per cent. By that time the pustular elements had disappeared leaving a dermatitis marked by bright purplish erythema, deeply purple lesions forming net-like patterns scaling and surrounding lichenification. The back down to the waist, the eyelids and surrounding skin as well as the scalp just above the ears had also become involved. Other features may be noted in Table 1.

Injections of bismuth were started on June 26, 1944, and were given once a week throughout his hospital stay. Chest x-rays taken at weekly intervals showed a gradual and satisfactory clearing of the pulmonic areas of density. A final diagnosis of primary atypical pneumonia was made. On July 17, 1944, the indolent ulcer on the left shin was covered by a skin graft, the end result of which was excellent. The eosinophile level fell to 3 per cent. A skin biopsy of an isolated, slightly nodular lesion was taken from below the right clavicle on August 9, 1944.

When the patient was evacuated on August 22, 1944, his general condition was very good and his skin exhibited definite signs of improvement. No raised lesions remained. Scaling had largely ceased, leaving brown pigmented skin of normal texture. This was particularly noticeable about the sacral, gluteal and ocular regions. Lichenification had regressed in all quarters and the purple hue had grown dull and brownish.

Pathological Report. It is estimated that the skin lesion of the chest appeared approximately three months before this biopsy was performed. Microscopically, the epithelium was generally of normal thickness with slight hyperkeratosis, except for one segment which showed extreme atrophy and parakeratosis. The rete pegs had sent small prolongations into the corium while the papillae were packed with lymphocytes and large endothelial cells. The corium contained a moderate amount of golden yellow pigment.

CASE VIII. When admitted to the hospital on March 29, 1944, this forty-one year old marine's chief complaint was a generalized scaling of the skin. He had spent five months on Guadalcanal, nine months in South Australia and finally six months in New Guinea. Ten weeks before admission both index fingers broke out with an eruption of small blisters. The dorsa of the feet and the ears soon developed the same condition. One week later a raised, red, well defined lesion developed on the right anterior chest at the costal margin. Gentian violet was applied to all the involved areas and within a few hours the ears, hands and feet became swollen and greatly irritated. Ten days later (about seven weeks before admission) "good sized bumps came out all over the skin." Thereupon, generalized scaling began including peeling of the palms and soles. Four weeks before entry he developed a fever of 101°F. Examinations of the blood for malaria and the stools for ova and parasites were negative. The white blood cell count was 14,150 with 28 per cent eosinophiles.

The family history and the past history were negative for allergy and skin diseases. In 1936, the patient contracted syphilis and received intravenous and intramuscular treatments regularly for the next two years. There was no associated rash. Despite the alleged consistent taking of atabrine while on the islands, he suffered two attacks of malaria on Guadalcanal and one in New Guinea. Treatment on those occasions with atabrine apparently caused no untoward effects.

The patient's build and nutritional aspects appeared normal. From head to toe his skin was desquamating with large scales and showed a general, diffuse, violet-tinged erythema. The largest nodule found was the one previously mentioned on the right chest. It was raised, well defined, oval, 1.5 cm. in length, violet and exhibited Wickham's striae. On April 8, 1944, this lesion was removed surgically for histological study. Similar although smaller, nodules were present over the backs of the hands, fingers and arms and on the trunk. Because the legs were most affected by the exfoliative process, it was difficult to determine the existence of nodules. The buccal mucosa and lips showed milk white,

lacy lesions and the tongue showed irregular, large, white plaques.

The laboratory studies revealed no anemia. A white blood cell count was 10,900 with 60 per cent polymorphonuclears and 18 per cent eosinophiles. Both the Kahn test and the urinalysis test were normal. A sedimentation rate was 26 mm. in one hour.

Treatment consisted of rest in bed, phenobarbital, colloidal baths, soothing lotions, atabrine in daily doses of 0.1 Gm. and weekly injections of bismuth subsalicylate.

For the first ten days he had an afternoon fever of about 99.4°F. Gradually the scaling and peeling diminished from above, downward. Finally, nodules could be detected on the legs in solid and reticular configurations. The ankle edema subsided but had not disappeared when he was transferred on May 1, 1944.

Pathological Report. The clinical aspects of the specimen have been discussed above. The lesion had been present for about two and one-half months. Histologically, the rete pegs of the epithelium were hypertrophied and completely surrounded by granulation tissue. The latter was heavily infiltrated with lymphocytes and a few leukocytes.

CASE IX. This soldier, a thirty-six year old cook, was admitted on March 7, 1944, because of skin lesions which had been developing for several months.

The patient landed in New Guinea in July, 1943, and had enjoyed good health until January, 1944. Early in that month he noticed an oval, red, raised, slightly itchy spot beneath his wrist watch strap on the volar surface. Within one month similar lesions spread over the forearm and appeared on the other arm. All units increased in size and tended to run together. In mid-February, 1944, the same process began on the inner aspect of the left ankle and extended up the leg; the right leg next followed suit. Finally, lesions developed at the base of the neck and over the upper anterior chest. During those weeks he observed an occasional blister on normal appearing skin.

The family and past histories were negative for dermatological, allergic and nervous diseases. He had taken atabrine regularly for eight months without any difficulty.

The patient was found to be high-strung, well developed, well nourished and in no discomfort. The lesions were most conspicuous on the flexor surfaces of the arms and medial aspects of the legs. White papules were present inside the corners of the mouth and white, lacy lesions were noteworthy on the lips. Besides a grouping of lesions along the lines of cleavage at the base of the neck, there were several distinctly linear lesions, 6 inches long and running down over the upper chest, more or less in line with his dog tag chain. Below the right shoulder blade, a circular lesion was found which measured 1 cm. in diameter, it was depressed and depigmented and showed a slightly violaceous areola.

The laboratory tests gave the following results: white blood cell count 9,750; eosinophiles 4 per cent; polymorphonuclears 71 per cent; urine and Kahn tests were negative and the sedimentation rate was 19 mm. in one hour. An x-ray film of the chest was normal.

The patient was given phenobarbital by mouth, a sulfur salicylic acid ointment to the lichenified and nodular expanses and a course of bismuth sub-salicylate injections.

Under observation the chart remained normal throughout his hospital stay. Small, violet nodular lesions developed to a minor extent over the dorsa of the feet. Two biopsies were performed on April 8, 1944. Before evacuation on May 16, 1944, the eruption about the neck had cleared the most of all. The purplish nodular elements had regressed considerably and assumed a brownish tinge. A marked bismuth line had developed in the gums without any symptoms. The labial and buccal lesions remained static.

Pathological Report. This specimen contained the lesion below the right shoulder blade which was described among the physical findings. It looked as though it might have been an old atrophied nodule.

Microscopically, there was moderate hyperkeratosis. The epithelium was thin and showed a slight tendency to verrucous formation. The rete pegs had been largely flattened. The corium was normal except for a few small areas of lymphocytic infiltration and a slight increase in vascularity. Very little brown pigment was present.

This second biopsy was from the lateral aspect of the right leg where nodular lesions had been progressing for about six weeks. A segment of a reticulation strand was selected which had passed through the violet and purple stages and had become quite brown. The microscope revealed marked hyperkeratosis with considerable blood present among the keratin layers. The epithelium was greatly hypertrophied including the rete pegs. The Malpighian layer appeared frayed where individual cells had separated off into the underlying corium. Inflammatory changes were present about the rete pegs and the sweat glands. Only a little brown pigment was found in some cells of the corium.

CASE X. A twenty-six year old cook was admitted on August 5, 1944, because of a widespread skin disorder of nine months' duration. The patient had been at the same base in northern Australia for the entire fourteen months of his overseas duty. In November, 1943, he noticed that a "heat rash" across his shoulder blades was behaving in an unusual manner. For years his skin had been prone to break out with tiny blisters whenever exposed to considerable heat and as a result there would be extreme itching. He would scratch and thus rupture the lesions which would proceed to dry up and disappear. The prodromal stage of the present illness is dated from the time (November, 1943) when the drying was first followed by residual, reddish, raised spots which were scaling. In the course of a week they turned purplish and in two more weeks became flat and smooth; finally, only white dots were left.

He attributed the eruption on his back to working in the sun without a shirt. Soon similar rashes appeared on the anterior chest, the arms and to a slight degree on his legs. There was no question in his mind but that the lesions were due to the steam heat from the mess kit cleaning drums over which he worked. On his days off, no eruption occurred even though he took sun baths and as he attained a coat of tan the incidence of the heat rash seemed lowered.

Four months before admission he was put to work at a field kitchen unit where the fire box was just off the ground. "The heat hit my legs through my pants just like pins and needles,"

he said. The individual blisters at those sites came out about three times their former size and the resulting purplish "bumps" began to run together. Trunk and arm lesions also became more marked. He thought his crotch region was spared because he wore shorts. Finally, the itching interfered with his sleep to such a degree that he reported on sick call and he was promptly sent to this hospital.

The histories of his mother, father, eleven siblings and relatives were negative for dermatological and allergic diseases. For many years the patient had "broken out all over with red spots" upon eating fifteen to twenty tomatoes in a day. He recalls no associated pruritus. While working on the family farm he had had similar eruptions intermittently over his extremities and chest which he called the "muck itch," supposedly due to dust, dirt and sweat. He never smoked excessively and had taken no atabrine or other drugs.

On physical examination the patient was found to be well developed and well nourished. Polygonal, shiny, flat topped papules of violet color were scattered generally over the arms, legs and trunk. They varied from pinhead size to three times larger. Many umbilicated papules were also present. The lesions tended to be grouped in patches, for instance over the shoulder blades, deltoid and parasacral regions. Excoriations were numerous and linear alignment of papules was noted repeatedly. On the extensor and lateral aspects of the legs the unit lesions had apparently coalesced into larger nodules. Scaling was most prominent there. The lower lip contained ramifying whitish striae. The axillary, epitrochlear and inguinal glands were slightly enlarged but not tender. The only other abnormality was the absence of knee jerks.

The results of the laboratory examination were as follows: The hemoglobin was 15.9 Gm; the white blood cell count was 10,800 with polymorphonuclears 61 per cent, lymphocytes 31 per cent, monocytes 4 per cent, eosinophiles 3 per cent and basophiles 1 per cent. The sedimentation rate was 8 mm. an hour while the Kahn and urine tests were negative.

Intramuscular bismuth was started at once and was repeated four times at four day inter-

vals. Thereafter, injections were given once a week. The dose was 2 cc. of subsalicylate in oil. Calamine lotion with 1 per cent phenol was used to relieve the itching.

On August 9, 1944, one skin specimen was excised from the upper abdomen and another from the right leg. Throughout the first three weeks of observation new lesions appeared every few days in widely scattered locations. For instance, one day a patch of typical papules broke out on the volar aspect of the right wrist. Two days later a palm-sized group of violet papulovesicles erupted over the lumbosacral region. Itching was intense and the tops of the eruptions were soon scratched off. The remaining papules became polygonal with shiny flat tops. The next day a 3 inch scratch mark was noted high on the right flank. Careful scrutiny revealed that it consisted of tiny papules in perfect alignment. The nodular lesions on the legs gradually regressed so that reticulation never developed. The patient was evacuated to the United States on September 1, 1944.

Pathological Report. The first specimen was taken from the upper abdomen and it contained small, polygonal, flat-topped violaceous papules. Microscopically, the epithelium appeared normal. The Malpighian cells were filled with pigment and there was minimal round cell infiltration around some of the small vessels in the corium.

The second biopsy from the leg included a purplish, scaling nodule which had begun as a vesicular lesion about four months previously. The sections showed increased thickness of the epithelium with marked hyperkeratosis. The rete pegs extended downwards in slender columns of cells. The epithelium contained several vesicles, in one of which were threads of fibrin plus a few monocytes. The corium was vascularized and filled with lymphocytes and a small amount of brown pigment was present.

COMMENTS

Since the cause of lichen planus is unknown and since these cases were so strikingly similar in their signs and histories, it was hoped that some understanding of the fundamental nature of the disease might be

derived from this study. The microscopic examinations added nothing to what is already well known about the pathological picture of lichen planus. A number of the sections were stained with Prussian blue. Failure of the pigment to take the stain

There was no reason to suspect that the disease might be contagious.

Certain features, however, do stand out from the mass of data presented in the case reports and they have been set down in Table II. The patients were for the most

TABLE II

SOME POINTS OF CLINICAL NOTE FROM THE HISTORIES OF THE TEN CASES OF LICHEN PLANUS

Case	Age	Past History of the Skin	Features of the Period Immediately Preceding the Onset of the Present Illness						Possible Precipitating Factors		
			Suppressive atabrine therapy, in months	Time spent in islands north of Australia, in months	Length of the prodromal stage, in weeks	Prodromal Signs and Symptoms			Sun	Heat	Fric-tion
I	42	Several minor attacks of poison ivy	6	6	12	Itching, vesicular eruptions over the volar aspects of the wrists and over inner thighs			..	+	
II	33	Mild intermittent athlete's foot	4½	4	2½	Itching, scaling, red spots starting on the inner thigh; also, peeling of the palms			..	+	+
III	19	Vitiligo	4	3½	10	"Sunburn" of the depigmented patches, including those covered by clothing			+	+	
IV	30	Mild intermittent athlete's foot	6	6	16	Vesicular rash on forearms for six days. Generalized itching. Sores on the lip			+	+	
V	25	Negative	2	2	4	Felt below par and lost weight			..	+	
VI	41	Mild intermittent athlete's foot	5½	5	14	Felt below par and lost weight			..	+	+
VII	37	Extensive "lichen planus" at the age of fourteen	3	3	4	Dryness and scaling of a scar on the left shin, followed by infection			+	+	
VIII	41	Negative	4	3½	1	Vesicular eruption on index fingers, feet, and ears			..	+	
IX	36	Negative	7	7	4	Itchy, dry, red spot under wrist watch strap			..	+	+
X	26	"Muck itch" from dirt and sweat. "Hives" from tomatoes	None	None	20	Vesicular eruptions leaving scaling, reddish spots			+	+	

indicated the absence of iron. Although the case reports do not indicate it, dietary histories were taken but no significant deficiencies were encountered. No important evidence to indicate an allergic mechanism was forthcoming and in no instance was there an apparent association between the onset of the illness and primary skin infection by either fungi or bacteria.

part in an older rather than a younger age group. Their past histories were not remarkable except that the patient discussed in Case VII had previously sustained a similar eruption. All but one had lived for months in the tropical islands north of Australia and had taken doses of atabrine. The disease characteristically came on insidiously with various kinds of pro-

dromata. Irritation by physical agents seemed to be a common denominator in the pathogenesis; for example, trivial trauma incurred by using a broom in his routine work produced the initial lesion in Case vi. The wearing of a wrist watch strap set off the overt disease in Case ix. The precipitating factor in Cases iii, iv, vii and x was probably sunburn.

It is impossible to draw any telling conclusions from the material at hand. Nevertheless, the author has a strong impression that the cause of this disease is intimately associated with the effects of climate on a peculiarly sensitive skin. What the sensitizing principle or principles might be, is (in the light of present evidence) so highly speculative that the matter will not be discussed herein.

SUMMARY

1. Ten unusual cases of lichen planus which developed in the Southwest Pacific Area are herewith presented.

2. The term "lichen planus hypertrophicus, retiformis" is suggested as a proper diagnosis for the first nine cases.

3. Though the cause of this disease remains obscure, the present study suggests that climate plus individual (constitutional) susceptibility may be of basic importance in the pathogenesis. Suspicions as to possible sensitizing factors are considered too speculative to mention. Irritation by external physical agents apparently constitutes an important precipitating factor in the disease process.

ADDENDUM

This paper was completed in the above form in September, 1944, at a time when it would have been highly undesirable to say that atabrine was strongly suspected as a major factor in the cause of atypical lichen planus. Even if atabrine had early been proven as the sole cause of atypical lichen

planus, its continued use on a grand scale would have been justified since the malarial problem was so tremendous and the dermatological aspect so relatively minute. The incidence of this skin disease was approximately 2 per 1,000 per annum in the Pacific Ocean area.

It will be noted in the text and Table II that nine of the ten patients had taken small doses of atabrine regularly over long periods before signs of lichen planus appeared. This is, of course, compelling evidence for the theory that sensitization to the drug was produced and that the skin and mucous membranes were the reacting tissues, but why did characteristic lesions develop in Case x in the absence of the atabrine factor? The author knows of another case similar to Case x which occurred in the Assam-Burma region. Furthermore, some cases of atypical lichen planus improve, despite the continued use of atabrine, while others fail to improve for weeks or months after atabrine has been terminated. A final point which also casts doubt on the all importance of atabrine is the fact that relatively few cases developed in certain tropical areas even though the exhibition of atabrine was being carried out in the accepted manner. The vast majority of the atypical lichen planus cases occurred in rather restricted geographic regions, especially New Guinea, the Philippines and the Assam-Burma border. The conclusion seems inescapable that other important factors besides atabrine must be carefully studied before the etiology of this disease can be established.

For further discussion see the article by Livingood and Dieuaide.²

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Neurogenic Pain Simulating Visceral Disease*

LYLE MOTLEY, M.D.

Memphis, Tennessee

SINCE all pain from whatever origin is reflected through the nervous system, it follows logically that abnormal conditions primarily affecting some part of the nervous system could produce pain of a character and distribution that could closely simulate the pain of visceral disease. However, it is apparent that this fact is frequently lost sight of by the medical profession, and we have observed that this leads to therapeutic sins both of omission and commission.

While neurogenic pain can assume any clinical type, we frequently have referred to us as diagnostic and therapeutic problems patients who present pain syndromes which in character and distribution strongly suggest visceral disease as the cause. The most common of these are arm and chest pains simulating cardiac pain, abdominal pain simulating cholecystic or gastrointestinal disease and loin and back pain simulating urinary tract lesions. While sciatic pain with low back pain does not simulate visceral disease, it will be included in this group because it has the same pathogenic factors and because it has been generally considered a "medical" disease, leading to the too frequent erroneous conception that it should be attacked with various drugs, injections of the nerve trunk, removal of teeth and tonsils as supposed focal infections, and occasionally ill advised major surgical procedures if the patient be a female.

CLINICAL TYPES

1. *Chest and Arm Pain.* In our experience this type of pain is seen most frequently on

the left side. This is probably due to the fact that a mild degree of pain occurring in the left chest arouses anxiety which if present on the right would not be associated with the idea of heart disease and would not cause the patient to consult a physician. This type of pain is seen in all degrees of severity from mild, and sufficient only to arouse the patient's anxiety concerning his heart, to severe pain of sudden onset very closely simulating acute coronary thrombosis. Its location may be vaguely in the left chest with some radiation to the shoulder and left arm, or it may have a definite location in the precordium with radiation to the left arm and hand. The clinical picture of cardiac pain may be simulated so closely that even one who has had extensive clinical experience has difficulty in reaching a satisfactory decision regarding the exact nature of the trouble. If the electrocardiographic tracing is normal, some difficulty is encountered in satisfactorily diagnosing the trouble; but the difficulties are greatly increased if there are abnormalities in the electrocardiogram coexisting with neurogenic pain. Proper solution of the situation requires clinical judgment and careful study.

An important factor in the differentiation of neurogenic pain from cardiac pain is awareness of the possibility of such a condition which should be kept in mind in every case of pain in the chest, shoulders and arms. The history is usually of help since neurogenic pain rarely has the typical crushing character that many cardiac pains have. Neurologic examination may or may not show changes in the reflexes, muscular atrophy, paresthesias, etc., depending upon

* From the Department of Medicine, School of Medicine, University of Tennessee, and the Lyle Motley Clinic, Memphis, Tenn. Read before the Gulf Coast Clinical Society, Mobile, Ala., October 2, 1947.

the character of the underlying disease as well as the extent of it. In the questionable cases, and therefore the most important ones from a diagnostic standpoint, obvious neurologic changes do not exist. Local tenderness in the chest wall or arm if present may be a help but often is absent. Two very important diagnostic aids are the electrocardiogram, of course, and x-ray examination of the cervical spine.

CASE I. A man age forty-six complained of severe pain in the precordium, radiating to the left shoulder and arm and of somewhat sudden onset. The pain had been paroxysmal for about forty-eight hours and his description of it was very suggestive of coronary occlusion. Physical examination was negative, blood pressure normal and electrocardiogram negative. Traction of the patient's neck relieved the pain, and pressure over the roots of the cervical plexus at the foramina intensified it. X-ray films of the cervical spine showed bony changes typical of ruptured intervertebral disc in the sixth interspace. Hemilaminectomy with removal of the extruded portion of the ruptured disc resulted in complete relief.

The foregoing case presented very few difficulties in diagnosis as the condition was quite typical. However, an occasional patient is seen in whom there exists neurogenic pain and whose electrocardiogram shows changes indicative of some degree of coronary disease. In such patients, sometimes only a long period of observation and the exercise of the best clinical judgment will determine if the patient's pain is of cardiac origin or is neurogenic, unless there are very distinctive and outstanding neurological changes.

CASE II. A sixty-four year old physician was referred for consultation. He had been kept in bed for five weeks with a diagnosis of coronary pain because of pain in the precordium radiating to the left mid-arm. The pain in his arm was of squeezing or crushing character. Bed rest had not influenced the pain although it was transiently relieved to a large extent by nitroglycerin. The electrocardiogram showed marked abnormalities with incomplete bundle branch block. After a period of observation the clinical

impression was that the patient's pain was probably not cardiac in origin, and x-ray films of the cervical spine showed evidences of a ruptured intervertebral disc in the fifth interspace. Head traction was applied, and within twenty-four hours the pain had disappeared but would recur if traction were left off for too long a period. After some days of continuous traction the patient returned home symptom-free and resumed his strenuous medical practice which he has continued without interruption for four years. Occasional recurrence of the pain necessitates application of traction for a short period which results in complete relief. The electrocardiogram remains unchanged.

Another misleading situation arises when a patient has pain suggestive of coronary disease with a demonstrable basis for neurogenic pain and no objective evidence of heart disease.

CASE III. A fifty-four year old man was referred because of precordial pain radiating to the left shoulder and arm, occurring on effort, particularly that requiring use of the arms and not relieved by nitroglycerin. An electrocardiographic tracing was entirely normal as was one made while the patient had pain deliberately produced by exertion. X-ray examination of the cervical spine showed the typical changes of a ruptured disc in the fifth and sixth interspaces. After a period of study our clinical impression was that the patient's pain was coronary in origin and not neurogenic. This impression was confirmed about two weeks later by the appearance of a frank acute coronary occlusion with typical electrocardiographic and other objective signs.

II. *Pain in the Lumbar Region and Loins.* Pain in this region, we find, has been most often erroneously diagnosed as some type of urinary tract disease. We find that although the patient has had no dysuria as part of his symptoms, urinary tract disease is diagnosed on the basis of some supposed abnormality detected in pyelo-ureterograms. We find a frequent error in this respect is the diagnosis of stricture or kink of the ureter. The common practice of injecting an opaque medium into the urinary tract and making only one x-ray film results in interpreting a normal peristaltic contraction

as a stricture of the ureter, and the normal fold of the ureter on deep inspiration as a kink. This is done even in the absence of any ureterectasis above the point of supposed stricture. The simple procedure of making serial urograms, as developed by Dr. Thomas D. Moore, would eliminate this error. Another source of incorrect diagnosis is the failure to keep in mind the possibility of neurogenic pain and the fact that pain in a given area does not of necessity mean pain in a viscus; another is the failure to distinguish between superficial tenderness or hyperesthesia and the deep tenderness present in visceral disease.

CASE IV. A woman age forty-three complained of pain at times of great severity in the left lumbar region and loin. Diagnosis of strictured ureter had been made two years previously and for treatment of this, twenty-two cystoscopic procedures had been carried out over this period of time with the idea of dilating the supposed stricture. Urologic investigation, including serial pyelo-ureterograms, showed a normal urinary tract. Examination showed marked tenderness beginning in the right costovertebral angle and extending around the flank to the abdomen. The tenderness appeared to be superficial, and neurologic examination showed hyperesthesia of the skin along the area of the tenth thoracic segmental innervation on the left. Torsion of the spine reproduced the patient's pain. X-ray examination of the vertebral column was negative. Spinal fluid was entirely negative and dynamics were normal. Paravertebral injection with novocaine of the ninth, tenth and eleventh nerves on the left resulted in complete disappearance of the pain as long as the effect of the novocaine lasted. Although no evidence of an intraspinal lesion could be demonstrated, an exploratory hemilaminectomy was done and no organic lesion was found. However, as the procedure was done under local anesthesia, identification of the involved nerves was possible and a section of the posterior roots was done. Since this procedure was done three years ago, the patient has had no pain and has been perfectly well.

The foregoing case is illustrative of a group of neurogenic pains for which no organic or inflammatory basis can be

demonstrated and which we must assume to be of a neuralgic type similar to the neuralgias of the cranial nerves.

CASE V. A school teacher age fifty-eight was referred by a urologist for investigation because of pain in the left lumbar region and flank of eighteen months' duration after his examination had shown no abnormality of the urinary tract. The patient had gone to him for removal of her left kidney, as a diagnosis had been made elsewhere of disease of the left kidney because of failure to visualize the kidney pelvis following intravenous injection of opaque medium. The clinical aspects of this patient were almost identical with those of the first case except the spinal fluid was xanthochromic, clotted spontaneously after withdrawal, and Queckenstedt's test showed a slight block in the spinal canal. Very little if any signs of cord compression were present, the only evidence being slight increase in activity of the left knee jerk and upon direct questioning admission by the patient of recent, slight weakness in the left leg. A laminectomy at the tenth thoracic level revealed an extramedullary meningofibroma which was removed with complete and permanent relief of pain.

III. *Abdominal Pain.* Neurogenic pain can be referred to the abdomen, leading to the diagnosis of gallbladder disease or appendicitis. An important diagnostic point in the consideration of abdominal pain is the fact that visceral disease of a degree and character sufficient to cause pain must of necessity cause some visceral dysfunction. Failure to take this point into consideration easily leads to errors in diagnosis when abdominal pain is present.

CASE VI. A woman age thirty-two consulted a surgeon because of pain very low in the right abdominal quadrant. Local tenderness was present and the surgeon made a diagnosis of "chronic appendicitis" and removed her appendix. Ten days after the operation, while the patient was still in the hospital, she complained of persistence of the same pain and the surgeon referred the patient to us as a diagnostic problem. A more detailed history showed that the abdominal pain had never been associated with any symptoms of intestinal dysfunction or nausea, but did show a relationship to pain in the right lumbosacral region radiating at

times to the right sciatic nerve. The latter pain was not considered by the patient to be of primary importance, and she did not stress it in the history given the surgeon. The history also included a severe fall in the past with pain and soreness in her back for some time. Neurologic examination showed a diminished right ankle jerk, a positive Lasègue's sign on the right and a positive Naffziger's sign. X-ray films showed narrowing of the fifth lumbar interspace, and the spinal fluid showed an increase in total protein to 80 mg. per cent; it was otherwise negative. A hemilaminectomy was done and the extruded portion of a ruptured intervertebral disc was removed with complete and lasting relief of the pain.

Situations similar to this patient's have been encountered by us many times, and the operations previously done have ranged from appendectomy to total hysterectomy.

PATHOLOGY

The character of this discussion is obviously such that a detailed consideration of the various types of pathology in the nervous system is not appropriate. Any mechanical or inflammatory change involving sensory nerve roots can produce the clinical pictures described. In our experience the most common cause of root pains is ruptured intervertebral disc with herniation of the nucleus pulposus and associated tissue changes. Within the past few years, familiarity with ruptured discs as a cause of sciatic pain has been widespread.¹ However, it has been only recently that we have become aware of the importance of considering a ruptured disc in the cervical region as a cause of chest and arm pain simulating coronary disease; and attention was first called to this by Semmes and Murphey² in 1941 and again by Whiteleather, Semmes and Murphey³ in 1944. We have found the incidence of this condition to be surprisingly high.

Next in importance are intradural extramedullary tumors of which meningeal fibroma and perineural fibroma are the most common. Of lesser incidence are sarcoma, fibroma, neurofibroma, chon-

droma, varices and angiomas, tuberculoma, etc.

Of the inflammatory changes, chronic arachnoiditis and pachymeningitis are probably the most important, although herpes zoster without eruption is an occasional cause of acute neurogenic pain and sometimes of chronic pain following the acute stage. The chronic ganglionitis of tabes is well known as a cause of neurogenic pain.

In the bony structure of the spine itself both benign lesions such as arthritic changes and osteomas, as well as malignant processes either primary or metastatic, can cause root pains. Tuberculous spondylitis can cause root pains months before x-ray changes in the bones appear.

Pain due to involvement of the cervical sensory roots is referred to the occipital region, the shoulder, arms and upper chest. In these areas it can simulate migraine or other types of headache, coronary pain and intrathoracic lesions.

Pain due to involvement of the upper thoracic sensory roots is often referred to an intercostal space while lower thoracic root pain is referred to the abdomen. If the pain is in the upper abdomen, it may simulate disease of the gallbladder, duodenum, stomach, colon or kidney. If referred to the lower abdomen (T_{10} to T_{12}), the pain may be mistaken for that of disease of the appendix, and pain from involvement of the lumbar or sacral sensory roots may be referred to the bladder, rectum, inguinal region and lower abdominal quadrants. In addition to sciatic and back pain, groin or lower abdominal pain occurs in 25 per cent of ruptured discs in the lumbar region.

DIAGNOSIS

Diagnosis of neurogenic pain is dependent to a large extent on consciousness of the possibility of such a condition when one is presented with a clinical picture of pain suggestive of visceral disease. There are certain characteristics of neurogenic pain that should be inquired into in every history in which pain is the outstanding symptom. The lesions mentioned as a cause

of root pains result in fixation of the nervous structures at the point of their location and, as a consequence of the absence of mobility, movements of the body involving bending of the spinal column very often will aggravate the pain or produce it. The same holds true with increase in intracranial pressure, and the history will often bring out the fact that the pain is aggravated by coughing, sneezing or straining at defecation. Since cutaneous paresthesias are often present along the distribution of the involved nerve, the history may show that the pressure of clothes produces discomfort.

It should not be necessary to remark on the importance of a careful general physical examination and all indicated laboratory and x-ray studies. A complete neurologic examination should be made with particular reference to certain diagnostic points. In ruptured discs in the cervical region manipulation of the neck will sometimes reproduce the pain, particularly slight tilting of the head toward the affected side and making downward pressure on top of the head. If the patient is seen while he has pain, firm traction upon the head will very often relieve the pain while traction is being applied. In the dorsal region hyperextension of the spine and forcible twisting of the spine may reproduce the patient's pain or intensify it. In the lumbar region Lasègue's test is valuable; it is carried out by flexing the thigh on the trunk with the leg extended. At any level Naffziger's test when positive is of value and consists of compressing the jugulars, preferably with a blood pressure cuff pumped up to a pressure of about 30 mm. of mercury for two minutes. A positive test reproduces or accentuates the pain. If the simple test is negative, frequently a cough will bring out the intensification or reproduction of the pain.

Spinal puncture should be done except in cases in which other evidence is unmistakably diagnostic, and Queckenstedt's test should always be performed when this is done. The total protein content of the fluid will usually be elevated when tumors or ruptured discs are present; however, a

normal protein figure does not eliminate these lesions from consideration. In the chronic inflammatory lesions there often are not any distinctive spinal fluid changes except, of course, in gumma or tuberculous changes in the spine.

X-ray examinations of the spine properly done are invaluable. Anteroposterior, lateral and oblique views should be made. When a ruptured intervertebral disc has existed long enough, typical bony changes appear manifested by narrowing of the interspace, spur formation on the anterior aspects of the bodies when seen in the lateral film and frequently osteophytes projecting posteriorly. Oblique views may show narrowing of the foramina. When the typical changes have not had time to occur, an important sign in the neck is segmental straightening of the vertebral column in lateral films and even reverse curvature, either of the whole neck or of segments. In the dorsal and lumbar regions narrowing of the interspaces with the body changes mentioned are the main signs although occasionally absence of normal curvature may be present alone. In tumors the classical signs of thinning or absence of the pedicles and widening of the interpediculate distance in anteroposterior films when present are of extreme value, but when absent have no negative value.

If no distinctive x-ray changes are seen, myelography should be done, preferably using pantopaque as a contrast medium. We have never observed any bad results from this procedure when carried out by our neurosurgeons in cooperation with our roentgenologist.

The treatment is primarily neurosurgical and will not be discussed here. However, in many patients with mild degrees of pain from ruptured discs in the cervical region, relief can be obtained by sleeping on a hard bed without a pillow, or, if this is ineffective, a period of bed rest with head traction carried out by an appropriate apparatus. A most important part of treatment is assuring the patient that his pain is not due to heart disease. Many of the milder pains

due to ruptured discs in the lumbar region will be relieved by a period of rest on a firm bed.

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Seminars on Hypertension

Treatment of Hypertensive Vascular Disease with Rice Diet^{*†}

WALTER KEMPNER, M.D.

Durham, North Carolina

THE treatment of hypertensive vascular disease with the rice diet¹⁻⁵ was suggested by observations made on the protein, fat and carbohydrate metabolism of isolated kidney cells under various pathologic conditions (cell injury and/or changes in pH, sodium bicarbonate concentration, oxygen tension and metabolizable substrate⁶⁻¹¹).

Until 1944 the consensus was that dietary treatment was useful in kidney disease but of no value in hypertensive vascular disease. "The diet in uncomplicated hypertension requires no essential change from the normal. There is no justification for restriction of protein intake, indeed, such restriction may result in anemia and other evidences of malnutrition. Likewise, in the absence of edema or paroxysmal dyspnea, the restriction of salt is unwarranted; claims that such restriction may lower the blood pressure have not been substantiated. Obesity should be avoided for the same reasons that apply to normal individuals and not because of any demonstrated relationship to hypertensive disease."¹² "No dietary treatment is known which has a specifically favorable effect on essential hypertension."¹³

The rice-fruit-sugar diet is more rigid than any of the fat-poor, salt-poor or protein-poor "hypertension" diets (the therapeutic possibilities and limitations of these will not be discussed here.) The rice diet contains in 2,000 calories not more than 5 Gm. of fat and about 20 Gm. of protein

derived from rice and fruit and not more than 200 mg. of chloride and 150 mg. of sodium. A patient takes an average of 250 to 350 Gm. of rice (dry weight) daily; any kind of rice may be used provided no sodium, chloride, milk, etc. has been added during its processing. The rice is boiled or steamed in plain water or fruit juice, without salt, milk or fat. If the sodium concentration of the plain water available is greater than 20 mg. per liter, distilled water should be used. All fruit juices and fruits are allowed, with the exception of nuts, dates, avocados and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. Not more than one banana a day should be taken. White sugar and dextrose may be used *ad libitum*; on an average a patient takes about 100 Gm. daily but, if necessary, as much as 500 Gm. daily should be used. Tomato and vegetable juices are not allowed. Usually no water is given and the fluid intake is limited to 700 to 1,000 cc. of fruit juice per day. Supplementary vitamins are added in the following amounts: vitamin A 5,000 units, vitamin D 1,000 units, thiamine chloride 5 mg., riboflavin 5 mg., niacinamide 25 mg., calcium pantothenate 2 mg. No other medication is given unless it is specifically indicated.

During the first period of "regulation" on the diet, the patient should be under constant medical supervision and blood

* From the Department of Medicine, Duke University, School of Medicine, Durham, N. C.

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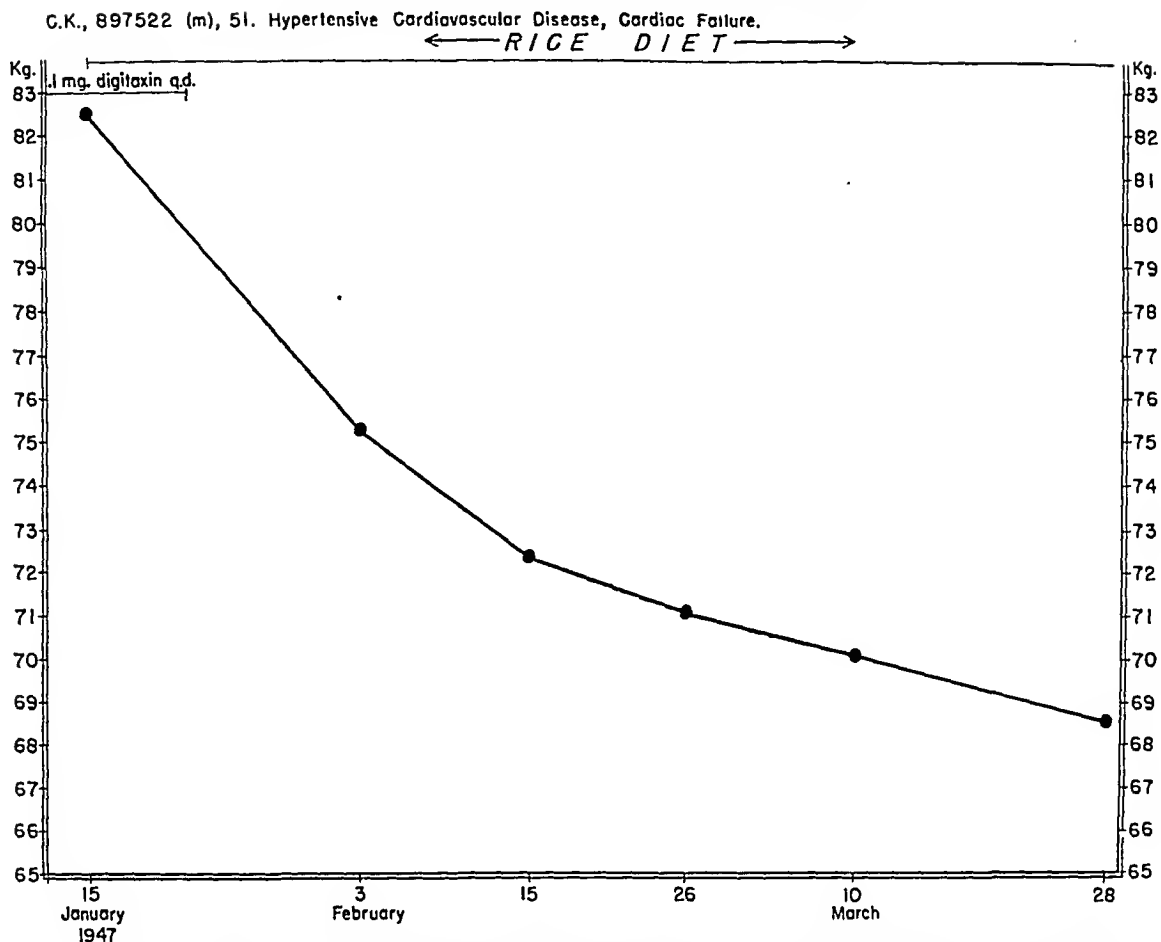


FIG. 1. C. K., male, fifty-one years of age. The patient had hypertensive vascular disease of seven years' duration, auricular fibrillation, cardiac failure of one year's duration, enlargement of liver and spleen and ascites. Previous treatment: digitalis, mercurials, ammonium chloride; codein; low salt, low fat, high protein diet; paracentesis 12 times in past year. January 15 to 21, 1947: Blood pressure, average, 174/97; NPN 44 mg. per 100 cc. blood; venous pressure 380 mm. of saline; total PSP excretion in two hours: 39 per cent. Rice diet started January 18, 1947, was strictly followed. All medication discontinued. On March 17, 1947, NPN 27 mg. per 100 cc. blood March 24 to 30, 1947: Blood pressure, average, 137/82. Ascites and edema unchecked by digitalis, mercurials, ammonium chloride, low salt high protein diet disappeared on rice diet without medication. There was a 14 Kg. weight loss in sixty-eight days.

and urine chemistry should be checked frequently.

Rest in bed, unless the severity of the condition demands it, is neither necessary nor desirable.

It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements; in this case the amount of rice, fruit and sugar must be increased unless reduction of weight is indicated. Another reason may be that the patient does not eat the full amount of his diet during the first period of

adjustment. The most frequent cause is the loss of visible or invisible edema; for example, one patient with marked edema lost 63 pounds in the first sixteen days on the diet (no digitalis, mercurials, etc., were given).⁵ Figure 1 shows the weight chart of another patient, a fifty-one year old physician, with hypertensive heart disease and auricular fibrillation whose persistent liver enlargement, ascites and edema had not improved in spite of intensive treatment with digitalis, mercurials, ammonium chloride, salt-poor diet and frequent paracenteses.

As a rule the diet should be continued without modification until those conditions

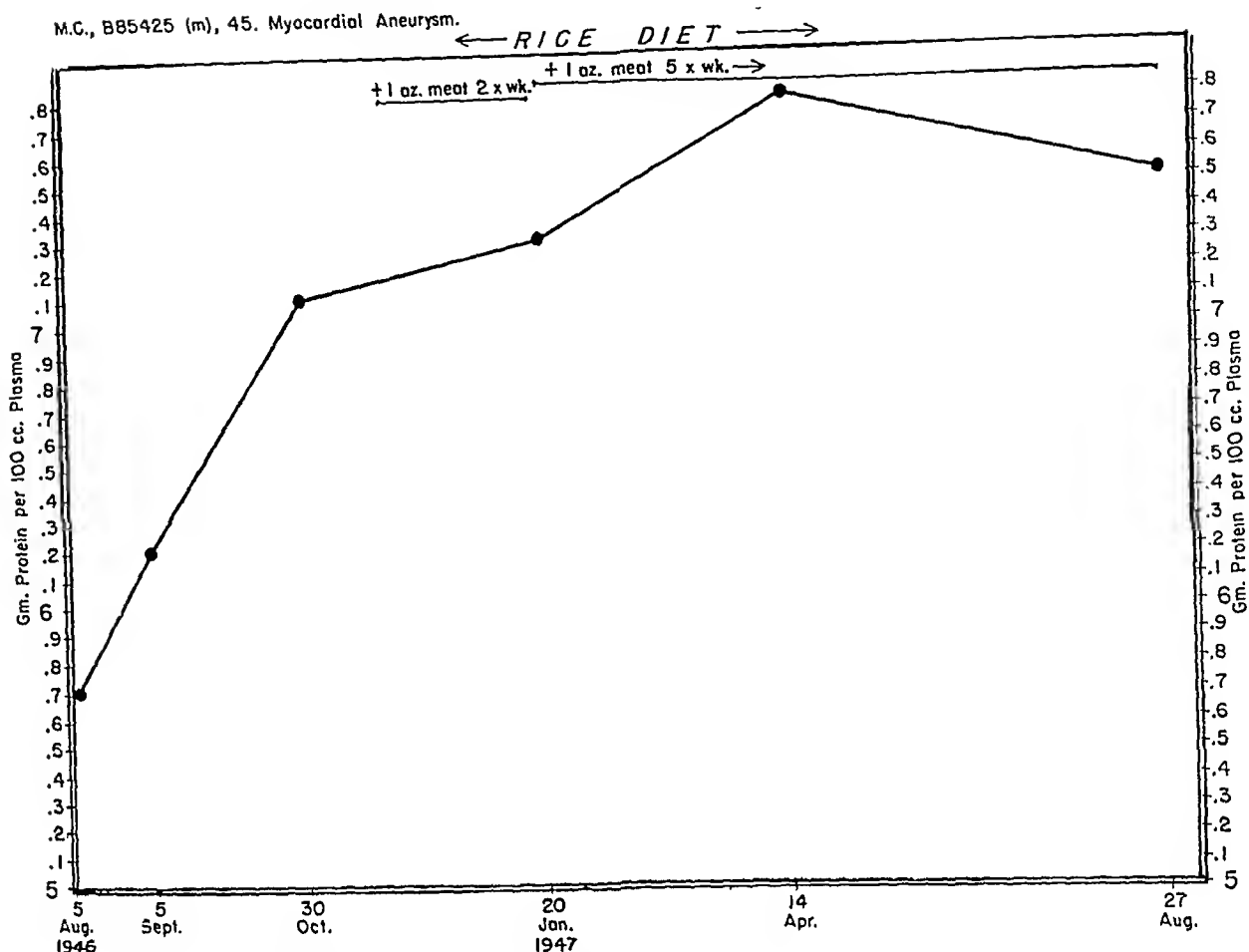


Fig. 2. Increase of plasma proteins on rice diet (for history see Figure 17).

which were the indication for its use have disappeared. Then small amounts of non-leguminous vegetables, potatoes, lean meat or fish (all prepared without salt or fat) may be added. But only so much additional food should be allowed as can be taken without producing undesirable changes in blood pressure, heart size, electrocardiogram, eyegrounds, non-protein nitrogen, etc. When a critical condition of heart, kidney or retina exists, the strict rice diet should be continued indefinitely provided that the equilibrium between intake and loss of those substances which are indispensable for the body is maintained.

CHEMICAL CHANGES PRODUCED BY THE RICE DIET

Nitrogen Metabolism. Because of the protein-sparing effect of carbohydrates, the

protein equilibrium is maintained in spite of the low protein content of the rice diet.

A minimum of 50 Gm. of protein (type of protein not specified) has been postulated as the so-called "wear and tear quota" necessary to cover the daily protein requirements. However, since this figure is derived from the total nitrogen excretion of fasting individuals, which is about 7 Gm. in the urine and 0.9 Gm. in the stools, it indicates only the amount of the body protein broken down in fasting ($7.9 \times 6.25 = 49.4$). In patients who have followed the rice diet for two months or more the daily urinary total nitrogen excretion is less than one third of that in fasting. It averages 2.26 Gm.⁵ If an allowance of 0.9 Gm. per twenty-four hours is made for the excretion of nitrogen other than that excreted in the urine, the total nitrogen loss in twenty-four hours is about 3.16 Gm. With a daily intake

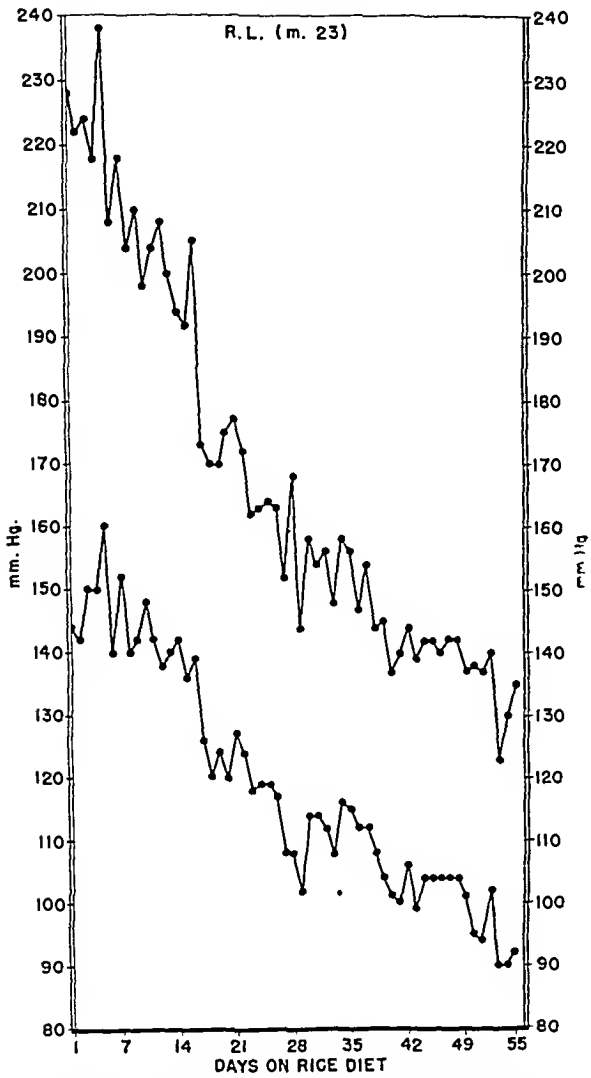


FIG. 3. R. L., male, twenty-three years of age. This patient had hypertensive vascular disease of three years' duration. He was previously treated with a "modified rice diet." EKG T₁ inverted. (Fig. 22.) Total PSP excretion in two hours: 2.5 per cent; NPN 79 mg. per 100 cc. blood; cholesterol 340 mg. per 100 cc. serum. There was advanced retinopathy. (Fig. 30.) Rice diet started December 18, 1945 and strictly followed for three months (8–21 mg. Cl per 100 cc. of urine). March 17, 1946: NPN 60 mg. per 100 cc. of blood; cholesterol 173 mg. per 100 cc. serum. _____ Decrease in blood pressure started in first week of rice diet.

of $3.16 \times 6.25 = 19.8$ Gm. of protein, these patients are in nitrogen equilibrium.

In fasting the daily urea nitrogen excretion in the urine is about 5.5 Gm. In the urine of patients who have followed the rice diet for two months or more the average daily urea nitrogen excretion is 1.1 Gm.⁵

In fasting the blood non-protein nitrogen and the blood urea nitrogen concentrations

TABLE 1 AVERAGE NPN AND UREA-N OF 261 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE (Initial NPN 20 to 45 mg. Per 100 cc. Blood)					
No. of Patients	Average Period of Treat- ment (Days)	NPN		Urea-N	
		Average Before Rice Diet	Average After Rice Diet	Average Before Rice Diet	Average After Rice Diet
		Mg. Per 100 cc.	Mg. Per 100 cc.	Mg. Per 100 cc.	Mg. Per 100 cc.
NPN and Urea-N Increased					
13	62	31	35	12.5	16.0
NPN Increased, Urea-N Decreased					
10	74	30	32	11.4	7.5
NPN Decreased, Urea-N Increased					
3	83	32	31	8.9	12.8
NPN and Urea-N Decreased					
235	109	34	26	14.4	7.3
Total					
261	106	34	27	14.1	7.8

are higher than normal; on the rice diet they are lower than normal.⁵ Table I shows the non-protein nitrogen and urea nitrogen in a series of 261 non-uremic patients with hypertensive vascular disease. The non-protein nitrogen before the diet ranged from 20 to 45 mg. per 100 cc. of blood; the average was 34 mg. After the diet it ranged from 18 to 45 mg.; the average was 27 mg. The urea nitrogen before the diet ranged from 4.8 to 30.3 mg. per 100 cc. of blood; the average was 14.1 mg. After the diet it ranged from 1.2 to 30.4 mg.; the average was 7.8 mg.

In starvation, hemoglobin and plasma protein concentrations decrease; on the rice

TABLE II

EFFECT OF HIGH AND LOW PROTEIN DIETS ON URINARY
TOTAL NITROGEN AND CREATININE OF NORMAL MAN
(FOLIN¹⁴)

	120 Gm. Protein Egg-Milk Diet (3rd Day)	6 Gm. Protein Cream- Starch Diet (7th Day)
Total nitrogen (mg. N per 24 hr.).....	16,800	3,600
Creatinine (mg. N per 24 hr.)..	580	600

TABLE III

EFFECT OF FASTING ON URINARY CREATININE AND CREATINE
OF NORMAL MAN (BENEDICT¹⁶)

	1st Day of Fasting (Weight 59.6 Kg.)	6th Day (Weight 55.9 Kg.)	12th Day (Weight 53.6 Kg.)
Creatinine (mg. N per 24 hr.)....	480	390	370
Creatine (mg. N per 24 hr.)....	0	130	120
Total creatine bodies (mg. N per 24 hr.)....	480	520	490

diet hemoglobin and plasma protein levels are maintained.⁵ (Fig. 2.)

The excretion of creatinine plus creatine (total creatine bodies) has been supposed to remain fairly constant in spite of variations in protein intake and nitrogen excretion. (Table II).

The excretion of the total creatine bodies does not decrease in one to twelve days of fasting. The creatine fraction increases. (Table III).

The excretion of total creatine bodies decreases markedly on the rice diet; the excretion of creatine does not increase. (Table IV).

The decrease in the excretion of total creatine bodies ranged from 7 to 48 per cent, averaging 29 per cent; the decrease in weight ranged from 0 to 11 per cent, with an average of 6 per cent.

TABLE IV

CREATININE AND CREATINE IN URINE OF TWENTY-TWO
PATIENTS (FIFTEEN MEN, SEVEN WOMEN) WITH HYPER-
TENSIVE VASCULAR DISEASE

	Before Rice Diet	After 35 Days (av.) on Rice Diet
Creatinine (mg. N per 24 hr.).....	480	346
Creatine (mg. N per 24 hr.).....	40	19
Total creatine bodies (mg. N per 24 hr.).....	520	365

TABLE V

TOTAL SERUM CHOLESTEROL OF 284 PATIENTS WITH
HYPERTENSIVE VASCULAR DISEASE

Initial Concentration (Mg. Per 100 cc. of Serum)		No. of Patients	Average Period of Treat- ment (Days)	Mg. Cholesterol Per 100 cc. of Serum (average)		
				Before Treat- ment	After Treat- ment	Change
110-218	Increased	18	123	156	180	+24
	Increased to 220 or over	4	93	208	240	+32
	Decreased or constant	61	109	195	157	-38
		83	110	187	165	-22
220-585	Increased or constant	10	146	250	262	+12
	Decreased	59	76	320	253	-67
	Decreased below 220	132	81	273	177	-96
		201	82	286	204	-82
110-585		284	90	257	192	-65

As far as the metabolism of kidney cells is concerned rice protein cannot be indiscriminately replaced by other protein. Proteins differ from each other in regard both to the type and the relative proportion of the various amino acids of which they are composed. They also differ in regard to the rate and degree of assimilation; 30 Gm. of a protein of which 88 per cent is assimilated may be preferable to 50 Gm. of a protein of which only 40 per cent is assimilated.

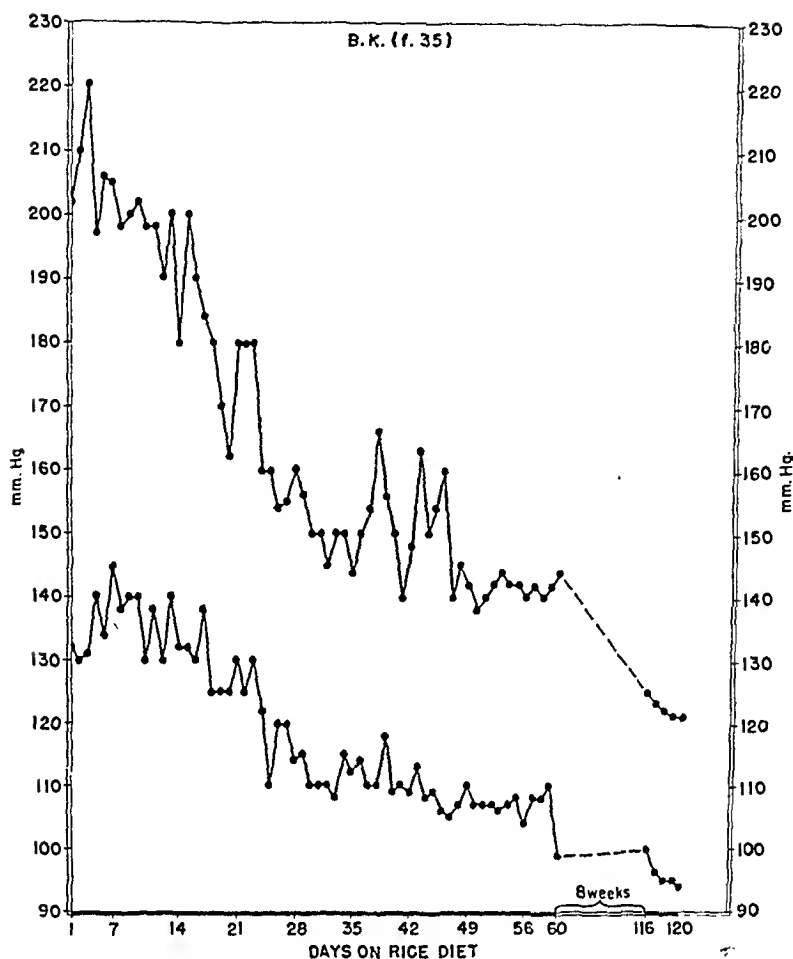


FIG. 4. B. K., female, thirty-five years of age. Patient had hypertensive vascular disease of eleven years' duration beginning during the eighth month of her second pregnancy. Of two brothers with hypertensive vascular disease, one had died at the age of thirty-seven (stroke). The patient had two retinal hemorrhages. Previous treatment: rutin, vitamin K, sedatives. Total PSP excretion in two hours 64 per cent; serum cholesterol 250 mg. per 100 cc. Rice diet was started April 23, 1947, and strictly followed (7-14 mg. Cl per 100 cc. of urine). No medication was given. A decrease in blood pressure began in third week on rice diet.

The factor of assimilation may be important not only because of the amount of protein that can be utilized to meet the body requirements but also because of the amount of the non-utilized protein fraction, the fate and rôle of which have yet to be determined.

Cholesterol. The relation between serum cholesterol and vascular disease (arteriosclerosis, coronary disease, vascular retinopathy, hypertensive vascular disease) has been the subject of extensive study.

Hypercholesterolemia, regardless of its primary cause in a given case, is just as

significant a metabolic disturbance as persistent hyperglycemia or hyperuricemia and should probably be considered as serious a disease, as far as potential consequences are concerned, as diabetes mellitus and gout.

Hypercholesterolemia decreases markedly with the rice diet.^{1,5,11} Table v shows the effect of the diet on the total serum cholesterol concentration of 284 patients with hypertensive vascular disease. Two hundred one of these patients (i.e., 70 per cent) had hypercholesterolemia (cholesterol concen-

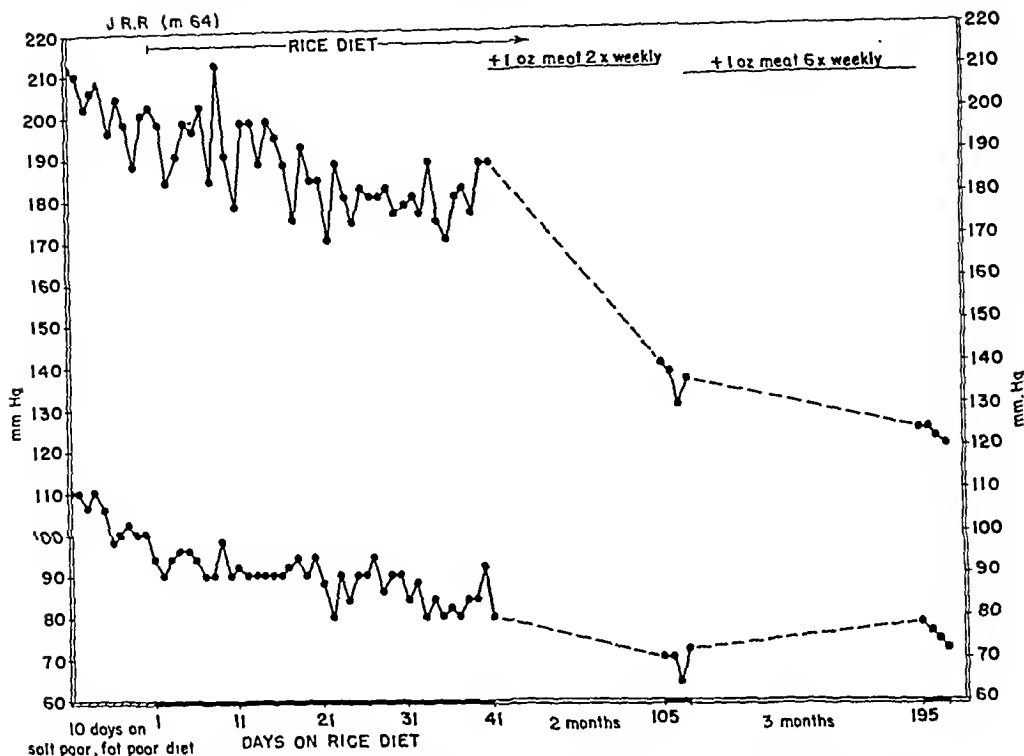


FIG. 5. J. R. R., a male, sixty-four years of age, had hypertensive vascular disease of six years' duration, four retinal hemorrhages and severe headache. He was treated previously with potassium thiocyanate. Total PSP excretion in two hours, 32 per cent. On October 7, 1946: Transverse diameter of heart, 15.2 cm.; diameter of great vessels, 10.5 cm.; weight, 62.8 Kg. Rice diet was started October 17, 1946, and strictly followed (4-9 mg. Cl per 100 cc. of urine). No medication was given. The patient was working and was asymptomatic. May 2, 1947: Transverse diameter of heart, 11.9 cm.; diameter of great vessels, 8.6 cm.; weight, 64.4 Kg. No retinal hemorrhages were present. There was reduction in heart size and in size of great vessels. (Fig. 8.)
Decrease in blood pressure was definite after 105 days.

tration of at least 220 mg. per 100 cc. serum) at the beginning of the diet.

Four patients whose serum cholesterol concentration was below the upper limits of normal had an increase to a hypercholesterolemic level (average before rice diet 208 mg. per 100 cc. serum, after rice diet 240 mg. per 100 cc. serum). One hundred thirty-two patients who had hypercholesterolemia had a decrease to a normal level (average before treatment 273, after treatment 177 mg. per 100 cc. serum). (Table v.)

Starke¹⁶ examined the concentration of free cholesterol and cholesterol esters in the serum of seventy-nine patients with hypertensive vascular disease who had a total cholesterol concentration of 220 to 463 mg. per 100 cc. of serum at the beginning of the diet. Free cholesterol and cholesterol esters

decrease on the rice diet in about the same proportion. (Table vi.)

Chloride, Sodium, Potassium. Therapeutic results with sodium chloride restriction such as those obtained by Allen and Sherrill¹⁷ and by Volhard¹⁸ were explained by Fishberg¹³ on the assumption that the unpalatability of the diet led to an inadequate caloric intake and thus to a reduction of the metabolic rate. According to Page¹⁹ the results obtained were due not to salt restriction but to "rest in bed and the psychotherapy of constant attention."

The treatment with the rice diet, which includes rigid sodium and chloride restriction, made it possible to determine the effect of a prolonged minimal intake of sodium and chloride on the concentration of these ions in blood, serum and urine.

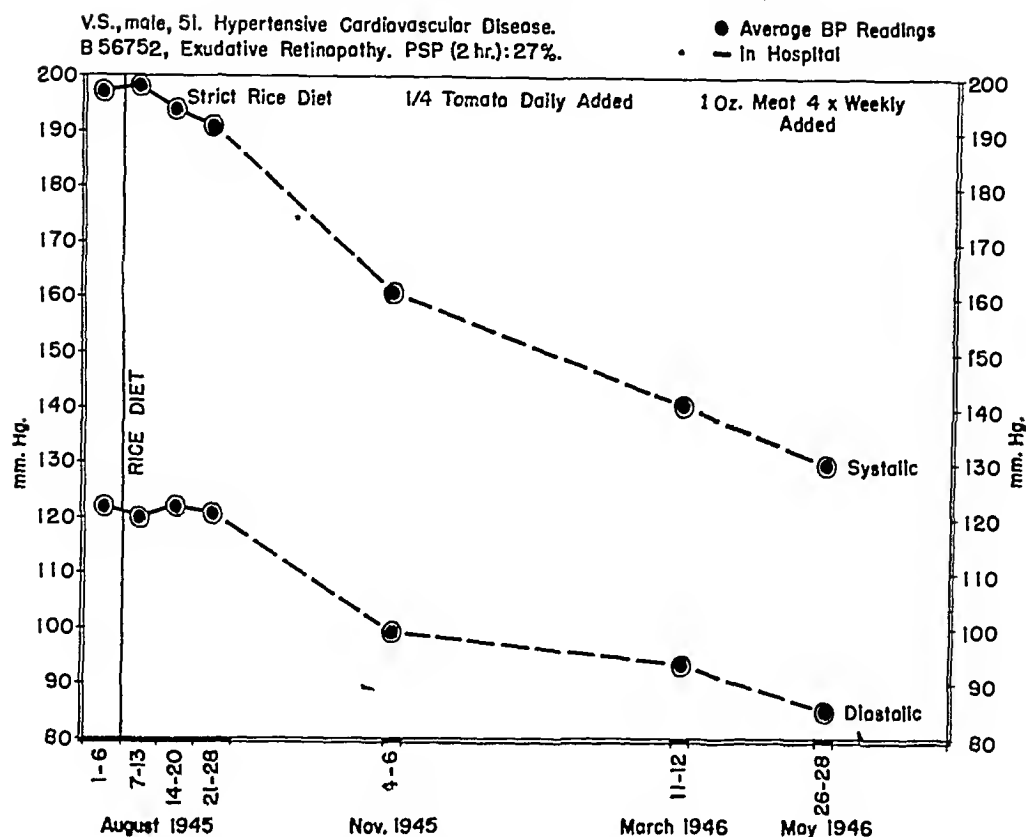


FIG. 6. V. S., a male, fifty-one years of age, had hypertensive vascular disease of eleven years' duration and retinal exudates. Previous treatment consisted of rest, sedatives and a "modified rice diet" for one month. Total PSP excretion in two hours: 21-33 per cent. Rice diet was started August 6, 1945, and strictly followed (5-20 mg. Cl per 100 cc. of urine). No medication was given. Working hours were restricted. There was a gradual decrease of blood pressure after the third month of rice diet.

In a series of 213 patients treated with the rice diet the lowest urine chloride concentration found was 48 mg. Cl per liter with a total urinary excretion of 18 mg. Cl in twenty-four hours in a patient with hypertensive vascular disease who had been on the rice diet for seventy days. The plasma chlorides were 93.1 mEq. (as NaCl: 544 mg. per 100 cc.). The average values of 381 determinations of the plasma chlorides in ninety-one non-uremic patients with hypertensive vascular disease or primary kidney disease were: before rice diet, 97.0 mEq. per 1,000 cc. of plasma; after forty-four days (average) of rice diet, 91.7 mEq. per 1,000 cc. of plasma.⁵

Table VII gives a comparison of the concentrations of chloride, sodium and potassium in the urine of persons on a normal diet

and of patients after two months on the rice diet.¹¹

The average values of the chloride, sodium and potassium concentrations and their ratios in whole blood, serum and urine in thirty-seven patients with hypertensive vascular disease treated with the rice diet for an average of thirty-six days are shown in Tables VIII and IX.

In thirteen of the thirty-seven patients there was "secondary" renal involvement; in twenty-four patients there was no evidence of renal involvement. The sodium chloride content of the diet of many of these patients had been limited before they were started on the rice diet. None of these patients was in renal failure with sodium chloride leakage.

The following average changes were found: In the urine there was a decrease in the sodium concentration of 99 per cent and in the chloride concentration of 96 per

TABLE VI
FREE CHOLESTEROL AND CHOLESTEROL ESTERS IN THE
SERUM OF 79 PATIENTS WITH HYPERTENSIVE VASCULAR
DISEASE

	Before Rice Diet	After 159 Days (Average) on Rice Diet
Free cholesterol (mg. per 100 cc. serum).....	80	61
Cholesterol esters (mg. per 100 cc. serum).....	205	146
Total cholesterol (mg. per 100 cc. serum).....	285	207

TABLE VII
URINE CHLORIDE, SODIUM, POTASSIUM ON "NORMAL" DIET
AND ON RICE DIET

	Normal Diet	Rice Diet (after 2 Months)
Chloride (Gm. Cl per 1,000 cc.)..	6	0.1
Sodium (Gm. Na per 1,000 cc.)..	4	0.01
Potassium (Gm. K per 1,000 cc.)..	2	3.0
Gm. Na/Gm. K Ratio.....	2	0.003

cent and an increase in the potassium concentration of 78 per cent. The sodium to potassium ratio decreased by 99 per cent and the chloride to potassium ratio by 97 per cent. There was a decrease of 79 per cent in the sodium to chloride ratio. All these changes are statistically significant.

In whole blood there was a statistically significant decrease of 4.3 per cent in the sodium concentration corresponding to an increase in hemoconcentration. There was a statistically significant decrease of 5.6 per cent in the chloride concentration. The sodium to chloride ratio remained constant. There was a statistically insignificant increase of 0.8 per cent in the potassium concentration and a statistically insignificant decrease of 3.4 per cent in the sodium to potassium ratio. The chloride to potassium ratio showed a decrease of 4.7 per cent (T value 2.1; probably statistically significant).

In the serum there was a statistically insignificant decrease of 0.7 per cent in the sodium concentration. Statistically significant changes in the serum were: a decrease of 6.2 per cent in the chloride concentration; an increase of 6.1 per cent in the sodium to chloride ratio; an increase of 11.3 per cent in the potassium concentration; a decrease of 8.6 per cent in the sodium to

TABLE VIII
CHLORIDE, SODIUM AND POTASSIUM CONCENTRATIONS IN WHOLE BLOOD, SERUM AND URINE OF THIRTY-
SEVEN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE BEFORE AND AFTER THIRTY-SIX DAYS
(AVERAGE) ON RICE DIET
(Average Values)

	Whole Blood			Serum			Urine		
	Before Rice Diet	After Rice Diet	Change %	Before Rice Diet	After Rice Diet	Change %	Before Rice Diet	After Rice Diet	Change %
	mEq./1,000 cc.			mEq./1,000 cc.			mEq./1,000 cc.		
Chloride.....	80.2	75.7	-5.6	100.8	94.5	-6.2	86.2	2.50	-96.2
Sodium.....	82.0	78.2	-4.3	142.8	141.7	-0.7	81.7	0.43	-99.2
Potassium....	49.5	49.5	+0.8	4.47	4.86	+11.3	64.4	88.6	+77.8

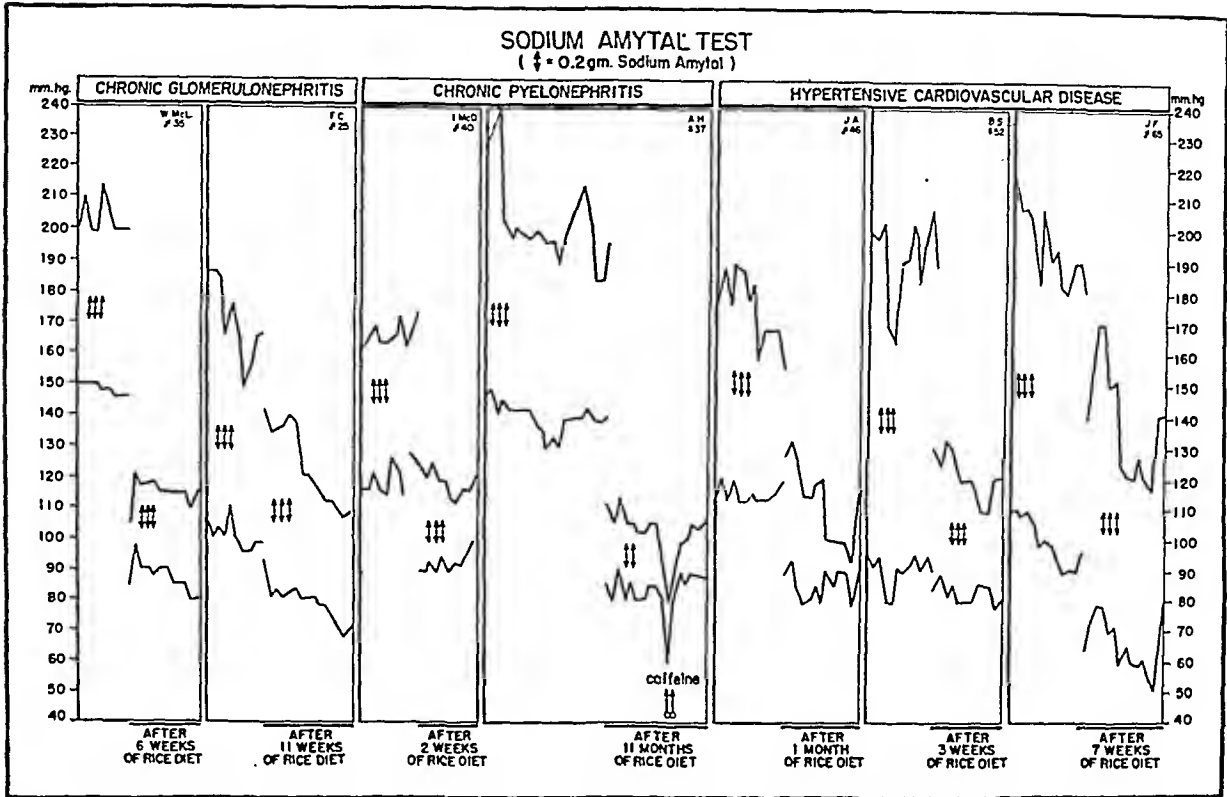


FIG. 7. Effect of 0.6 Gm. of sodium amytal on blood pressure before and after rice diet. (Reprinted from *North Carolina M. J.*, 6: 65, 1945).

TABLE IX
SODIUM, CHLORIDE, POTASSIUM AND SODIUM CHLORIDE RATIOS
IN WHOLE BLOOD, SERUM AND URINE OF THIRTY-SEVEN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE
BEFORE AND AFTER THIRTY-SIX DAYS (AVERAGE) ON RICE DIET
(Average Values)

	Whole Blood			Serum			Urine		
	Before Rice Diet	After Rice Diet	Change %	Before Rice Diet	After Rice Diet	Change %	Before Rice Diet	After Rice Diet	Change %
Na/K	1.67	1.61	-3.4	32.7	29.4	-8.6	1.66	0.006	-99.3
Cl/K	1.63	1.55	-4.7	23.1	19.6	-14.0	1.71	0.03	-96.9
Na/Cl	1.02	1.03	+1.6	1.42	1.50	+6.1	0.92	0.18	-79.4

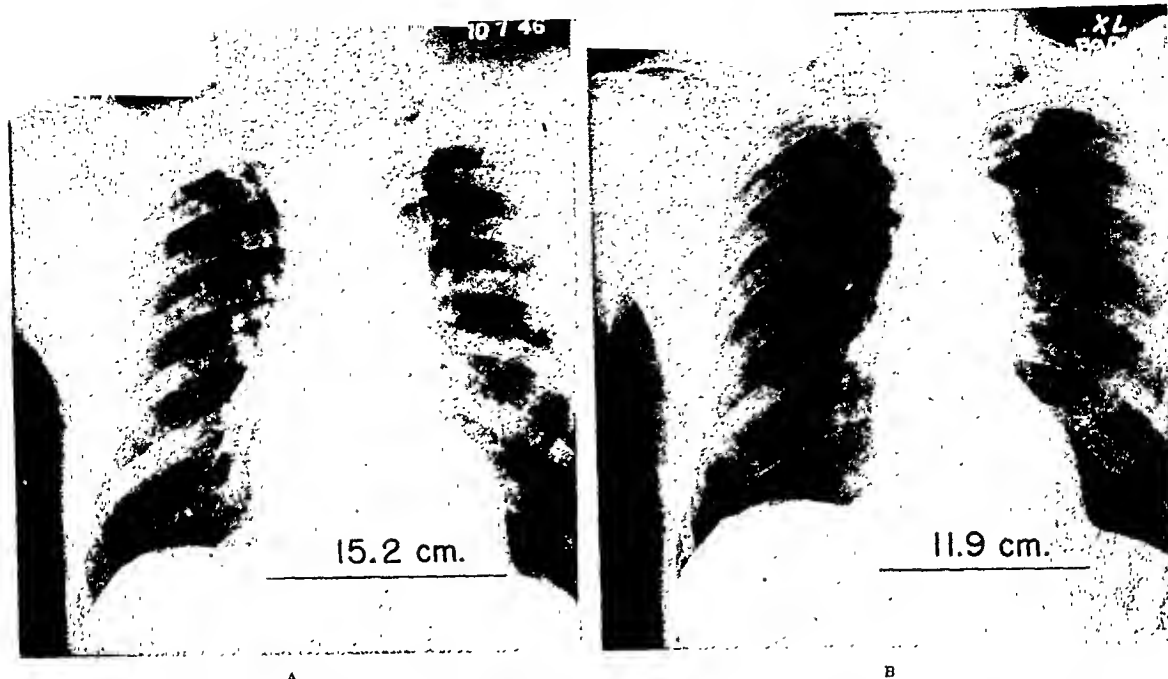
potassium ratio; a decrease of 14.0 per cent in the chloride to potassium ratio.

Sulfate, Phosphate and Ammonia Excretion in Urine. Chloride, sulfate and phosphate account for about 85 per cent of the acid excreted in the urine on a normal diet.

As Tables x and xi show the inorganic

sulfate excretion in patients on the rice diet decreases by 80 per cent; the inorganic phosphate excretion decreases by 60 per cent.²⁰

Ammonia is formed in the kidney by oxidative deamination of amino acids; blood and tissue acids reaching the kidney



A

B

FIG. 8. J. R. R., a male, sixty-four years of age, had hypertensive vascular disease of six years' duration, four retinal hemorrhages and severe headache. He was previously treated with potassium thiocyanate (three years). A, October 7, 1946; Blood pressure 212/110; weight, 62.8 Kg.; total PSP excretion in two hours, 32 per cent. Rice diet was started October 17, 1946, and strictly followed (4-9 mg. Cl. per 100 cc. of urine). No medication was given. B, May 2, 1947; Blood pressure 122/74; weight, 64.4 Kg. No appreciable drop in blood pressure after forty-one days of diet. The patient was working. A definite drop in blood pressure was noted after 105 days of diet. (Fig. 5.) The patient was asymptomatic and retinal hemorrhages had disappeared. There was a reduction in heart size with change in transverse diameter of 28 per cent and a reduction in size of great vessels with change of 22 per cent.

TABLE X

SULFATE EXCRETION IN URINE OF FOURTEEN PATIENTS
(TEN MEN, FOUR WOMEN) WITH HYPERTENSIVE
VASCULAR DISEASE—NO RENAL FAILURE

	Range		Average		De-crease (%)
	Before Rice Diet	After 36 Days (Average) on Rice Diet	Before Rice Diet	After 36 Days (Average) on Rice Diet	
	(Mg. S in 24 Hr.)		(Mg. S in 24 Hr.)		
Total sulfate.....	761-471	254-58	592	126	79
Inorganic sulfate....	547-362	165-40	452	81	82
Ethereal sulfate...	328- 52	115-15	140	45	56

as salts of fixed base are converted there into ammonium salts and excreted as such in the urine; thus the fixed base in the body is conserved. Under pathologic conditions (e.g., at lowered oxygen concentrations) the rate of deamination of amino acids and of ammonia production in the kidney is

TABLE XI

PHOSPHATE EXCRETION IN URINE OF SEVENTEEN PATIENTS
(THIRTEEN MEN, FOUR WOMEN) WITH HYPERTENSIVE
VASCULAR DISEASE—NO RENAL FAILURE

	Range		Average		De-crease (%)
	Before Rice Diet	After 34 Days (Average) on Rice Diet	Before Rice Diet	After 34 Days (Average) on Rice Diet	
	(Mg. P in 24 Hr.)		(Mg. P in 24 Hr.)		
Inorganic phosphate	1055-501	435-170	761	289	62

decreased.^{6,8} The acid must be excreted in the urine as salts of fixed base, the fixed base in blood and tissues decreases and uremic acidosis follows.^{9,10} In considering the significance of the figures in Tables x and xi one might speculate about the possibility of forestalling an accumulation of acids in blood and tissue fluids by restricting

TABLE XII
AMMONIA EXCRETION IN URINE OF TEN PATIENTS WITH
HYPERTENSIVE VASCULAR DISEASE

mg. NH ₃ per twenty-four hr.		Change (Average)
Before Rice Diet	After 28 Days (Average) on Rice Diet	
479	139	-70%

sulfur and phosphorus in the diet, i.e., by reducing the quantity of acid formed. Or, in cases in which the kidney although functioning under pathologic conditions has retained its ability to form ammonia, one might speculate about the possibility of reducing the rate of oxygen consumption by reducing the rate of ammonia production. The amount of oxygen thus saved might lead to an increase in the oxygen concentration at the surface of kidney cells where the supply of oxygen is diminished. As Table XII shows the ammonia excretion in the urine is decreased by the rice diet.

Table XIII compares the quantities of solids excreted in the urine on the rice diet and on a normal diet.

Discussion of the "Active Principle" of the Rice Diet. Since the first reports on the rice diet (1944), the importance of the rigid restriction of protein, fat, sodium and chloride has been stressed. Up to that time the therapeutic effect of this diet on blood pressure, heart size, electrocardiogram, eye-grounds, non-protein nitrogen, edema, etc., had been determined in 150 patients with acute and chronic nephritis and hypertensive vascular disease.^{1-4, (5)}

Grollman and Harrison (1945) believe that the effect of the rice diet is due to its low sodium content. They repeated some experiments with the rice diet on rats in which renal hypertension had been induced by the thread compression method. They confirmed our finding that the diet leads to marked blood pressure reduction. Since the hypotensive effect was not obtained when the strict rice diet was changed by the addition of NaCl (not of KCl), this

TABLE XIII
URINARY EXCRETION (GM. IN 24 HR.) ON "NORMAL" DIET
AND ON RICE DIET

	Normal Diet	Rice Diet (2 Months or More)
Total nitrogen	15.0	2.3
Urea nitrogen	12.0	1.1
Uric acid nitrogen	0.3	0.08
Total creat. nitrogen	0.6	0.4
Ammonia nitrogen	0.6	0.1
Sodium	4.0	0.01
Potassium	2.0	3.0
Chloride	7.0	0.1
Inorganic phosphate	1.0	0.3
Total sulfate	0.80	0.13
Inorganic sulfate	0.72	0.08
Ethereal sulfate	0.08	0.05

hypotensive effect was ascribed by the authors to the sodium restriction.²¹

Selye and Stone (1946) kept the sodium chloride content of the diet high and varied the protein content. They produced nephrosclerosis with heart enlargement in rats by unilateral nephrectomy, lyophilized anterior pituitary gland and the substitution of a 1 per cent NaCl solution for drinking water. Each group of rats was fed exclusively on one of the following foods: skeletal muscle, cardiac muscle, "purina fox chow," peas, lentils, corn, lima beans or rice. They found that the degree of nephrosclerosis and the final organ weights were lowest in the rats fed with rice.²²

Dock (1946) compares the relative infrequency of arteriosclerosis of the coronary arteries in the Chinese and Italian population with the high incidence of this disease in the American army and stresses the importance of cholesterol. "Diets high in cholesterol, such as the American servicemen had while in this country, may hasten the process and lead to death decades earlier than if the individual had been on a diet poor in cholesterol." "As hypertension and cholesterol metabolism become better understood and controllable there is every reason to believe that there will be a decline from the present appalling death rate from coronary disease to the insignificant level

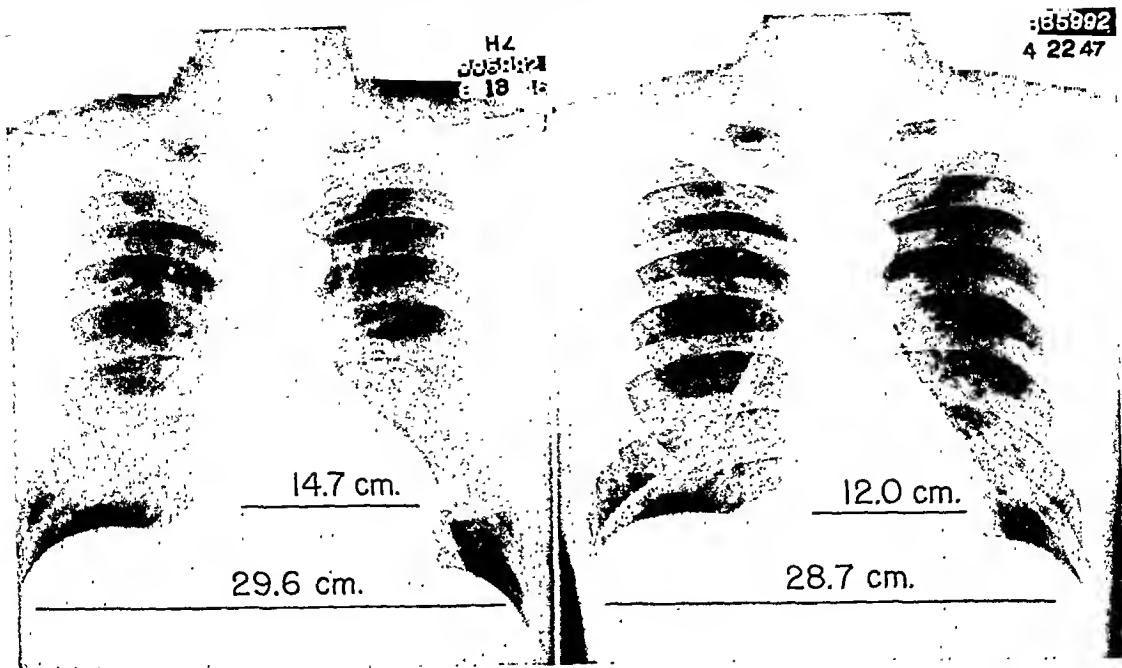


FIG. 9. I. S., a male, forty-one years of age, had hypertensive vascular disease of three years' duration, retinal hemorrhages and exudates. Previous treatment consisted of rest and phenobarbital. Total PSP excretion in two hours, 60 per cent. A, August 12 to 13, 1946; Blood pressure 220/150; cholesterol 290 mg. per 100 cc. serum; EKG T_1 diphase to inverted; weight, 72.5 Kg. Rice diet was started August 17, 1946 and strictly followed for two months (2-7 mg. Cl per 100 cc. of urine); then moderately well followed (35-36 mg. Cl per 100 cc. of urine). No medication was given; the patient was working. B, April 21, 1947; Blood pressure 128/88; cholesterol 155 mg. per 100 cc. of serum; EKG T_1 upright. Retinal hemorrhages and exudates had disappeared; weight 56 Kg. There was decrease in blood pressure and reduction in heart size with change in transverse diameter of 22 per cent.

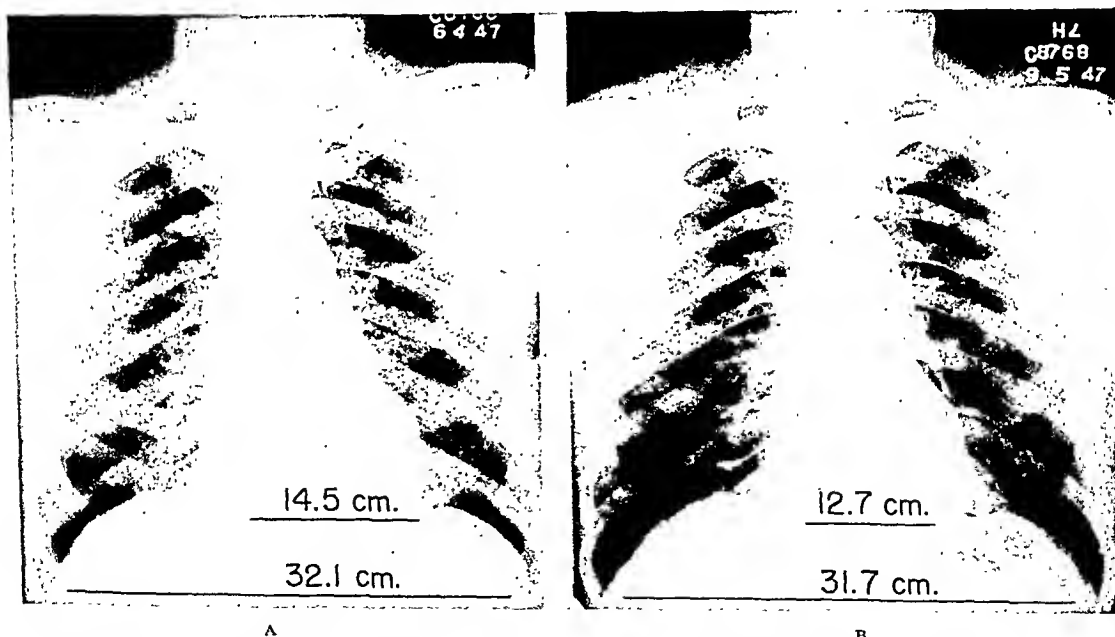


FIG. 10. H. H., a male, sixty-three years of age, had hypertensive vascular disease of at least two and one-half years' duration and a stroke 1946. Previous treatment consisted of aminophyllin, rest, sedatives, weight reduction. Total PSP excretion in two hours 56 per cent. A, June 3, 1947; Blood pressure 217/124; weight, 76.3 Kg. Rice diet was started June 7, 1947, and strictly followed for three months (9-23 mg. Cl per 100 cc. of urine.) No medication was given. B, September 7, 1947; Blood pressure 170/98; weight, 70.7 Kg. There was a decrease in blood pressure and a reduction in heart size with change in transverse diameter of 14 per cent.

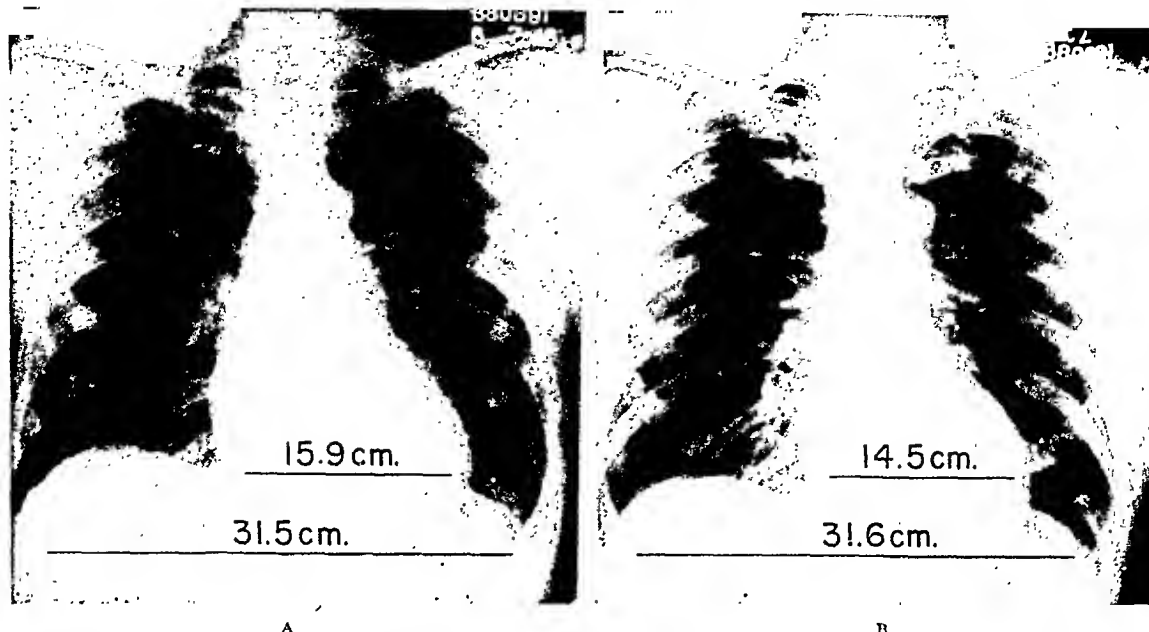


FIG. 11. R. H., a male, fifty-two years of age, had hypertensive vascular disease of three years' duration and pulmonary edema. Was treated with digitalis, mereuhydrin, aminophyllin and morphine. Total PSP excretion in two hours 39 per cent. A, June 8, 1946; Blood pressure 222/130; weight, 78.7 Kg. Rice diet was started June 12, 1946, and strictly followed for four months (11–22 mg. Cl per 100 cc. of urine); then moderately well followed (43–48 mg. Cl per 100 cc. of urine). All medication except digitalis was discontinued at beginning of rice diet. Digitalis was discontinued 7–24–46. B, May 31, 1947; Blood pressure 178/106; weight 71.2 Kg.; the patient was asymptomatic and resumed his practice as surgeon. There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 10 per cent.

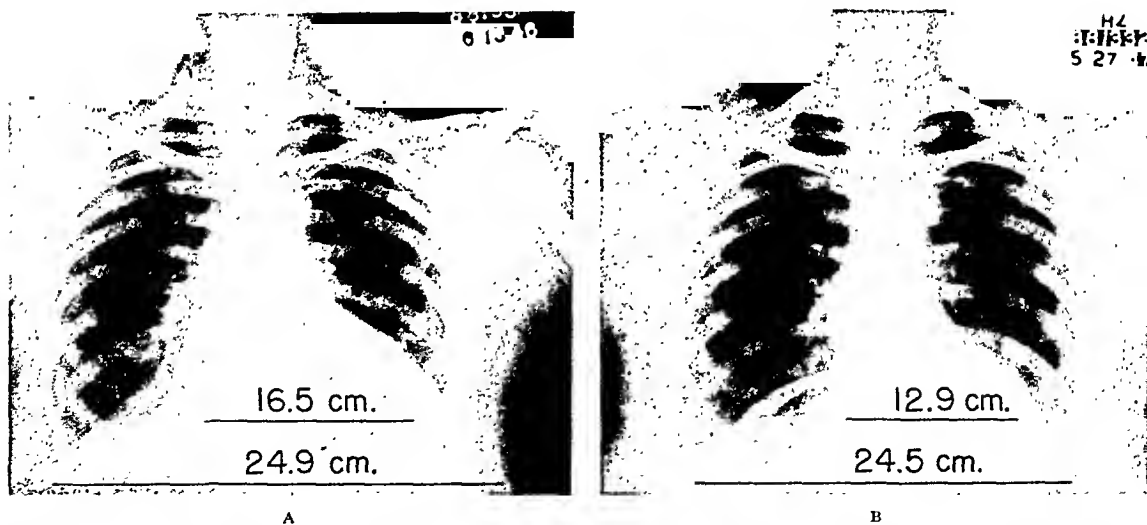


FIG. 12. A and B. G. H., a female, forty-five years of age, had hypertensive vascular disease of at least three years' duration, retinal hemorrhages and exudates. Total PSP excretion in two hours, 52 per cent. A, June 14, 1946; Blood pressure 258/138; EKG T₁ inverted; weight, 64.8 Kg. Rice diet was started June 20, 1946, and strictly followed for four months (4–13 mg. Cl per 100 cc. of urine); then moderately well followed (26–31 mg. Cl per 100 cc. of urine); no medication was given. The patient was active. B, May 28, 1947; Blood pressure 184/98; EKG T₁ upright; weight 59.6 Kg. No retinal hemorrhages or exudates were present. There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 28 per cent.

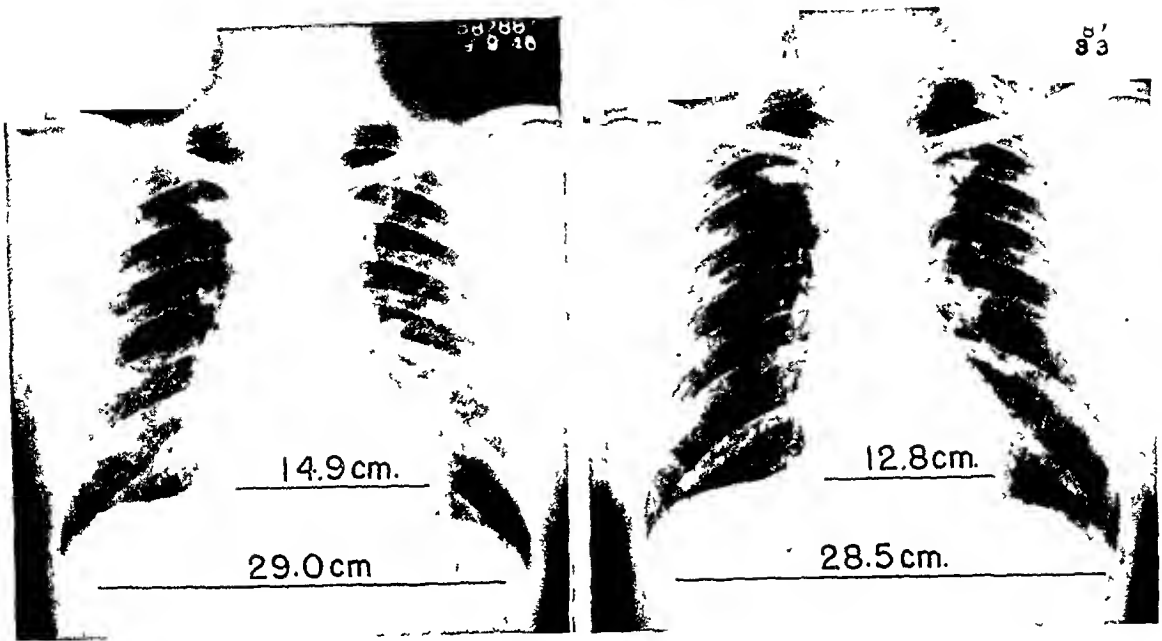


FIG. 13. A and B. O. P., a male, forty-one years of age, had hypertensive vascular disease of five years' duration with severe headache. September 5, 1946; Blood pressure 186/122; EKG T_1 inverted; total PSP excretion in two hours 79 per cent; weight 68.7 Kg. Rice diet was started September 9, 1946; no medication was given. He was asymptomatic and able to do his work. On April 1, 1947; Blood pressure 150/100; EKG T_1 upright; weight, 66.4 Kg. There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 16 per cent.

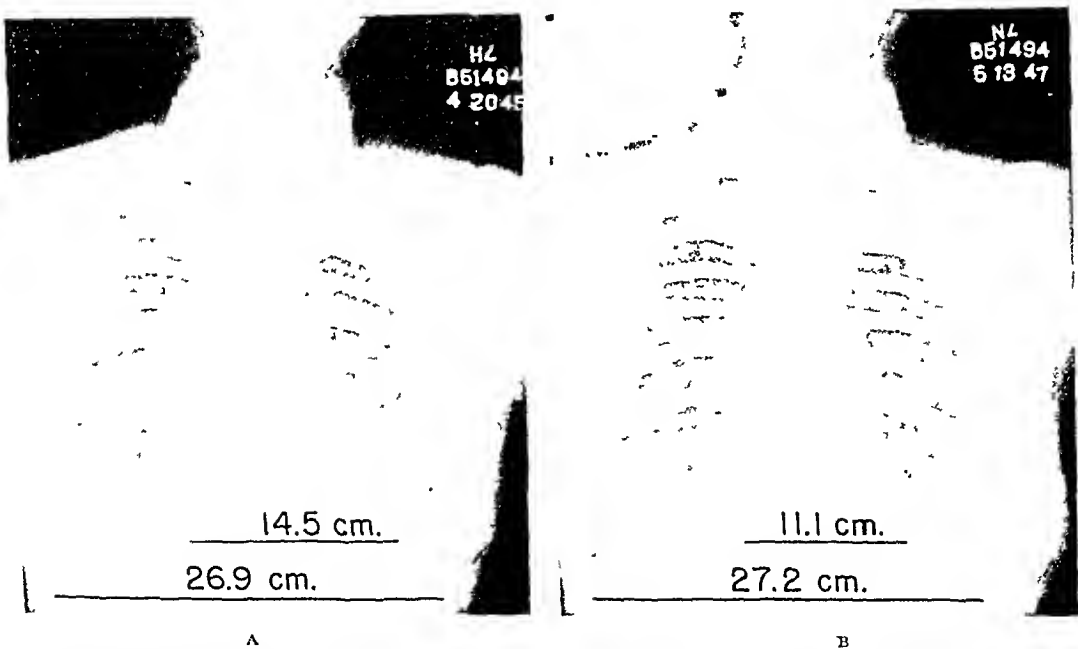


FIG. 14. A and B. R. Z., a female, fifty-three years of age, had hypertensive vascular disease (of at least five years' duration) and diabetes mellitus. Previous treatment: reduction diet (25 pound weight loss). April 19, 1945; Blood pressure 202/140; weight 53 Kg.; BMR $\times 45$ per cent; total PSP excretion in two hours 62 per cent, sugar, 231 mg. per 100 cc. blood (no insulin). Rice diet was started April 22, 1945; it was well followed through May, 1945, and from January, 1946 to February, 1947 (7-15 mg. Cl per 100 cc. of urine). No digitalis was given. From August, 1945 to December, 1946, 10-30 units of insulin were given daily. May 13, 1947; sugar, 113 mg. per 100 cc. blood (no insulin). May 14, 1947; Blood pressure 224/112; weight, 50 Kg.; BMR -10 per cent. There was reduction in heart size with change in transverse diameter of 31 per cent in spite of persistence of high blood pressure.

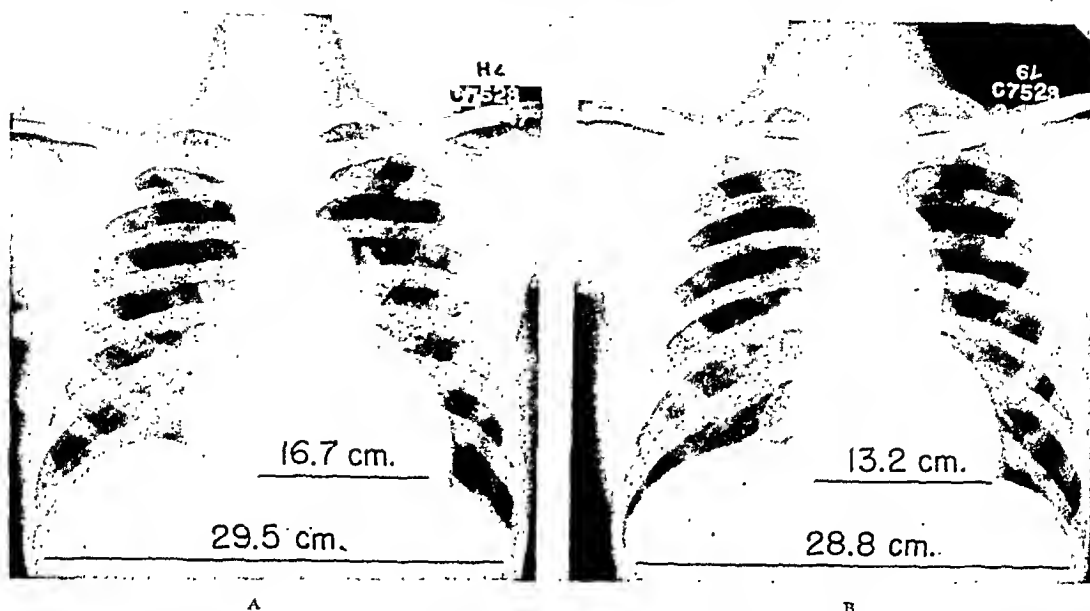


FIG. 15. A and B, J. P., a male, forty-two years of age, had hypertensive vascular disease of ten years' duration and cardiac failure of six months' duration. Previous treatment: sympathectomy in 1940 and from 1940 to 1946 potassium thiocyanate and phenobarbital. In 1946 pituitary irradiation was given; since 1946, digitalis, mercurials and sedatives (0.6 Gm. sodium amytal daily). May, 1947: Total PSP excretion in two hours, 32 per cent; venous pressure 195 mm. of saline. May 17 to 27, 1947; Blood pressure 220/152; weight 60.3 Kg. Rice diet was started on May 17th and strictly followed for four months. All medication was discontinued on May 17th except digitalis which was discontinued June 9, 1947. September 8, 1947; Blood pressure 214/148; weight 57.1 Kg. A reduction in heart size occurred with change in transverse diameter of 27 per cent, in spite of persistence of high blood pressure.

now prevailing in other populations such as the Chinese."^{23,24}

G. Dick and Schwartz (1947) measured the arterial pressure in dogs in which hypertension had been produced by a nephrosclerosis which followed the intravenous administration of streptococci. At the time when the rice diet was started the hypertension had been maintained for two to four years. Dick and Schwartz found an average decrease of the mean arterial pressure from 181.6 to 138 mm. Hg after eight weeks on the diet. They conclude: "It appears that the Kempner regime is capable of causing significant lowering of the arterial blood pressure of dogs made hypertensive through the induction of nephrosclerosis. The role of weight loss, salt restriction, and nitrogen balance in this result requires further study."²⁵

INDICATIONS AND CONTRAINDICATIONS

The apparent simplicity of the rice diet has not infrequently proved a handicap.



FIG. 16. M. C., a male, forty-five. Planogram of myocardial aneurysm. (See Figure 17.)

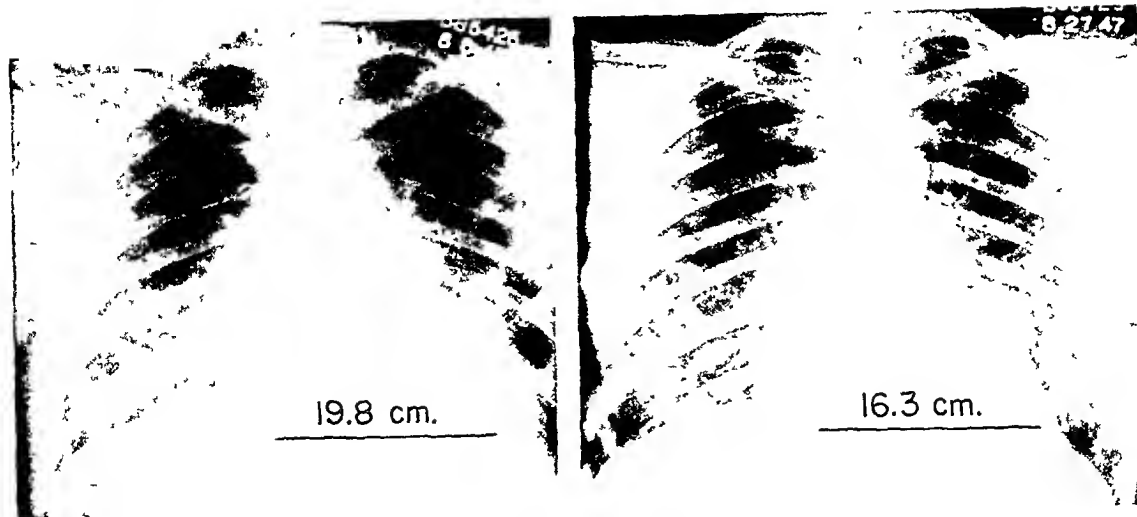


FIG. 17. A and B, M. C., a male, forty-five years of age, had a history of hypertension in 1944, myocardial infarction in 1945, followed by myocardial aneurysm.²⁶ There was progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia (Fig. 2), hypocalcemia, albuminuria, decubitus ulcer and dyspnea. Previous treatment: (four months' hospitalization) low-protein, salt-poor diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose, paracentesis. Rice diet was started August 7, 1946, and strictly followed; paracentesis August 13th; oxygen inhalation. No medication was given except digitalis which was discontinued October 10, 1946. Blood pressure August 6, 1946 was 138/94, August 27, 1947, 118/94. Advanced myocardial failure unchecked by previous intensive treatment was compensated by rice diet. The patient became asymptomatic and reduction in heart size occurred with change in transverse diameter of 21 per cent.

We have seen patients who had been treated with the diet just because the manometer had shown blood pressure figures above normal and in whom tumors, infections, etc. had been overlooked.

The rice diet is indicated in all serious instances of acute and chronic nephritis;^{1-5,11} in heart failure which does not respond to the customary treatment with salt restriction and drugs;^{1-5,11,26} in arteriosclerotic and hypertensive vascular disease with cardiac, cerebral, retinal or renal involvement.^{1-5,11,26}

The rice diet should be tried in uncomplicated hypertensive vascular disease when a more liberal regimen (fat-poor, salt-poor diets, weight adjustment, restriction of activities, regulation of bowel habits, sedation, etc.) has failed.

The rice diet should be used as a therapeutic test before sympathectomy is considered. If the dietary treatment proves ineffective, it can be discontinued.

In cases complicated by peptic ulcer the rice diet has to be modified. The rice is well tolerated, but raw fruit should be avoided

and only cooked, strained fruit should be used. Water or dialyzed milk may be substituted for the fruit juices.

The rice diet is not contraindicated in cases complicated by diabetes mellitus. It may in fact have a special value because of the dangerous rôle played by hypercholesterolemia in this disease.²⁷ It was expected that in order to maintain the previous blood sugar levels larger amounts of insulin would have to be given. We found instead that in many cases the blood sugar decreased on the rice diet and the insulin dose had to be reduced.

The rice diet is contraindicated unless frequent checks of the patient's blood and urine chemistry are possible. This is of especial importance in patients with renal sodium chloride leakage as the following history may illustrate:

A patient with hypertensive heart disease (Figs. 18 and 19) had been on the diet for seven months. He had followed it very strictly. After three weeks on the diet the serum chloride was 95 and the serum

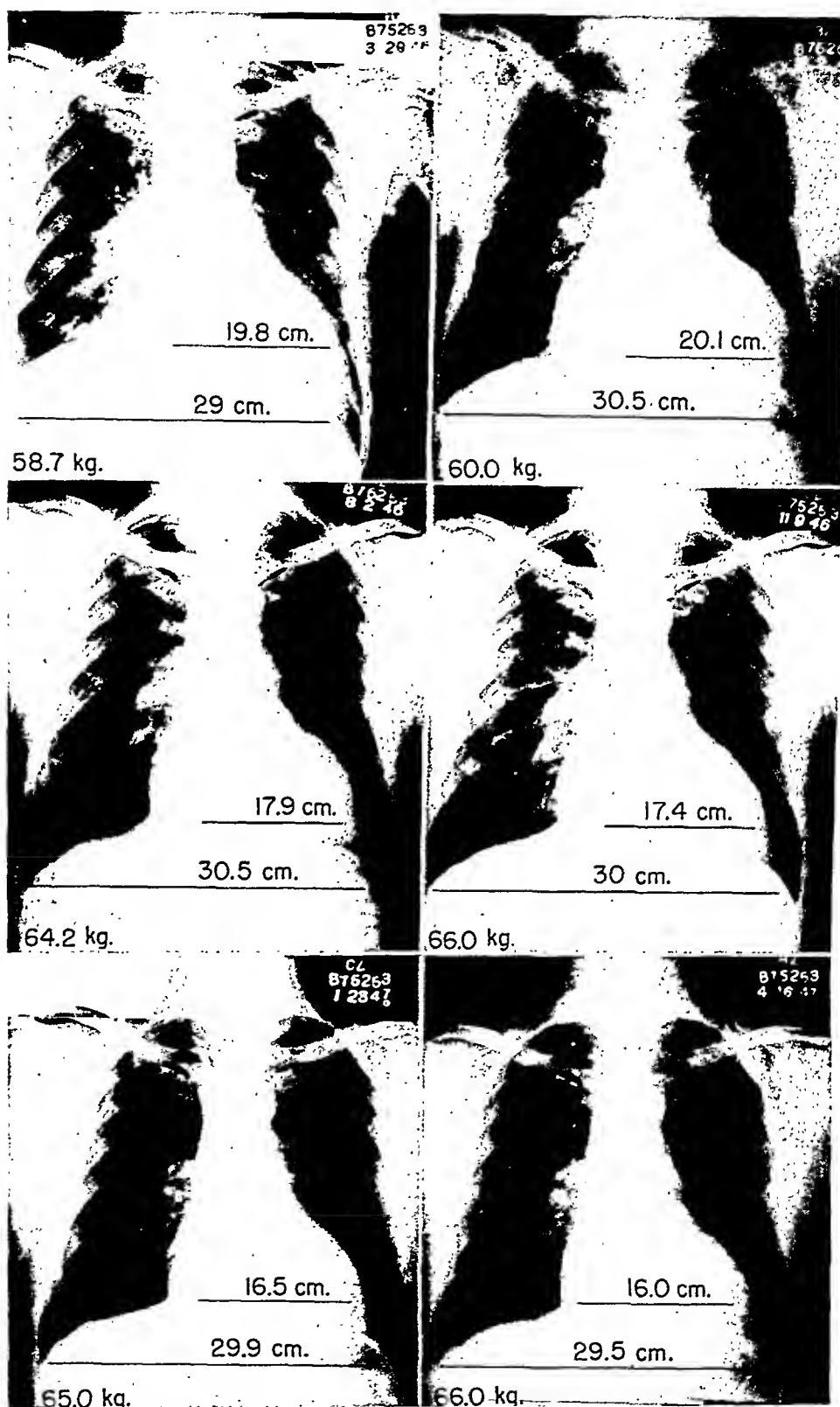


FIG. 18. P. K., a male, fifty-six years of age, had a history of nephrolithiasis, hypertensive vascular disease of more than ten years' duration, nephrectomy (left) in 1940, heart disease of three years' duration; left bundle branch block; dyspnea, edema. Previous treatment: salt-poor diet, digitalis, squill, salyrgan, mercupurin, ammonium chloride, sedatives. Total PSP excretion in two hours, 24 per cent; NPN 45 mg. per 100 cc. of blood; blood pressure 145/90. Rice diet was started April 3, 1946, and strictly followed (1-10 mg. Cl per 100 cc. of urine). All medication discontinued except digitalis. Digitalis was discontinued April 20, 1946. There was a weight gain of 7.3 Kg and a gradual decrease in heart size.

sodium 135 mEq. per liter; after four months, 87 and 138 mEq. respectively. From the fifth month on he had felt well and had been completely asymptomatic. One evening, after some hours work at carpentry, he suddenly became unconscious and remained so for many hours. His hands and feet were extremely cold and, on regaining consciousness, he felt very weak and "faint." The attending internist who was familiar with the treatment made a diagnosis of stroke. However, on the addition of a few vegetables to his diet, all the symptoms disappeared and three days later when the patient was brought to our hospital, examination of the serum revealed a chloride concentration of 69 and a sodium concentration of 125 mEq. per liter.

CLINICAL CHANGES PRODUCED BY THE RICE DIET

A great many patients on the rice diet have experienced relief from headache, giddiness, fatigue, dyspnea and substernal pain. Such subjective improvement has not been accepted as evidence of successful therapy. Only measured results such as decrease in blood pressure, reduction in heart size, loss of edema and reversion of electrocardiogram or eyeground changes have been used to determine the effect of the treatment.

The therapeutic results in eighty patients with acute or chronic primary kidney disease and in 130 patients with hypertensive vascular disease were reported in 1945.⁵ By 1946 one hundred patients with primary kidney disease and 222 patients with hypertensive vascular disease had been treated with the rice diet.¹¹ This paper is limited to the changes obtained in patients with hypertensive vascular disease.

The effect of the diet has been determined in 500 patients most of whom were seriously ill and had failed to respond to other forms of treatment. The diet has been ineffective in 178 of these 500 patients if we include twenty-six patients who were in a critical condition when started on the diet and who died after an average period of thirty-nine

days. In 322 of the 500 patients the diet has proved beneficial, i.e., it has produced one or more of the following effects: decrease in "mean" arterial blood pressure of at least 20 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; a change in T_1 from completely inverted to upright; disappearance of severe retinopathy.

Blood Pressure. Five hundred patients (207 women, 293 men) with hypertensive vascular disease whose "mean" arterial pressure (sum of systolic and diastolic pressures divided by 2) was 125 mm. Hg or more were treated with the rice diet. The age ranged from nineteen to seventy-three (average, fifty-one) years. Two hundred twenty-nine patients had signs of renal involvement; in 271 no conclusive evidence of renal involvement was found.

The systolic blood pressure levels before treatment ranged from 154 to 264 mm. Hg; the average was 199 mm. The diastolic blood pressure levels ranged from 72 to 172 mm. Hg; the average was 117 mm. Hg.

After they were regulated on the diet under our supervision, most of the patients followed the diet at home, returning at intervals of two to six months for reexamination.

The blood pressure was considered improved if the "mean" arterial pressure had decreased by at least 20 mm. Hg.

The results are summarized in Table xiv. The figures given are averages of the daily readings of three to twenty-four (average, eight) days before and after treatment.

Of the 229 patients in whom the diagnosis of hypertensive vascular disease with "secondary" renal involvement was made, twenty-five died six to ninety-six days (average, thirty-nine days) after the diet was started. Of the 271 patients without evidence of renal involvement, one patient died thirty-six days after the rice diet was started.

Table xv shows the difference in the percentage of improvement when these twenty-six patients who died are not included.

TABLE XIV
EFFECT OF RICE DIET ON BLOOD PRESSURE OF 500 PATIENTS
WITH HYPERTENSIVE VASCULAR DISEASE
(PERIOD OF DIET 4-898 DAYS)
AVERAGES

No. of Patients	Blood Pressure		Change in Systolic and Diastolic Pressure	Change in "Mean" Arterial Pressure	Days on Rice Diet
	Before Rice Diet	After Rice Diet			
With Renal Involvement <i>Hypertension Not Improved</i>					
74 25	206/121 226/147	191/117 Died	-15/-4	-9.5	71 39
<i>Hypertension Improved</i>					
130	207/121	159/98	-48/-23	-35.5	81
Without Evidence of Renal Involvement <i>Hypertension Not Improved</i>					
89 1	186/109 248/138	167/102 Died	-19/-7	-13	68 36
<i>Hypertension Improved</i>					
181	193/113	147/93	-46/-20	-33	85
Total <i>Hypertension Not Improved</i>					
163 26	195/114 227/147	178/109 Died	-17/-5	-11	69 39
<i>Hypertension Improved</i>					
311	199/116	152/95	-47/-21	-34	83

TABLE XV
PERCENTAGE OF POSITIVE AND NEGATIVE BLOOD PRESSURE
RESULTS (A) INCLUDING AND (B) NOT INCLUDING
TWENTY-SIX PATIENTS WHO DIED

A		B	
229 Patients with		204 Patients with	
Renal Involvement	%	Renal Involvement	%
Not improved.....	44	Not improved.....	37
Improved.....	56	Improved.....	63
271 Patients without		270 Patients without	
Evidence of Renal		Evidence of Renal	
Involvement	%	Involvement	%
Not improved.....	33	Not improved.....	33
Improved.....	67	Improved.....	67
All 500 Patients	%	All 474 Patients	%
Not improved.....	38	Not improved.....	35
Improved.....	62	Improved.....	65

TABLE XVI
INFLUENCE OF THE LENGTH OF TREATMENT WITH THE
RICE DIET: BLOOD PRESSURE CHANGES IN PATIENTS
WITH HYPERTENSIVE VASCULAR DISEASE

	Period of Treatment	
	4-34 Days	35-898 Days
	With Renal Involvement	With Renal Involvement
Number of patients.....	86	143
Not improved.....	49 = 57%*	50 = 35%†
Improved.....	37 = 43%	93 = 65%
	Without Evidence of Renal Involvement	Without Evidence of Renal Involvement
Number of patients.....	109	162
Not improved.....	47 = 43%	43 = 27%‡
Improved.....	62 = 57%	119 = 73%
	Total	Total
Number of patients.....	195	305
Not improved.....	96 = 49%	93 = 30%
Improved.....	99 = 51%	212 = 70%

* Including 13 patients who died.

† Including 12 patients who died.

‡ Including 1 patient who died.

TABLE XVII
CHANGES IN DIASTOLIC PRESSURE OF 406 PATIENTS WITH
HYPERTENSIVE VASCULAR DISEASE
INITIAL DIASTOLIC PRESSURE OF 100-159 MM. HG.

	No. of Pa- tients	Per- cent- age	Average Change
Decrease of 30 mm. Hg or more	52	13	-36
Decrease of 20-29 mm. Hg....	101	25	-24
Decrease of 10-19 mm. Hg....	158	39	-14
Decrease of 0-9 mm. Hg.....	77	19	-5
Increase of 1-22 mm. Hg.....	18	4	+7
Total.....	406	100	-16.7

Figures 3 to 6 show typical blood pressure curves of patients on the rice diet.

The length of time required for the blood pressure to decrease varies from four days to ten months. The part played by the

TABLE XVIII

EFFECT OF RICE DIET ON HEART SIZE: AVERAGE CHANGES IN TRANSVERSE DIAMETER OF HEART
IN 286 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

	No. of Patients	Per- cent- age	Period of Rice Diet (Average) Days	Diameter of Chest (Averages)				Transverse Diameter of Heart (Averages)			
				Before Rice Diet	After Rice Diet	Change		Before Rice Diet	After Rice Diet	Change	
							% (Diameter of Chest of Smaller Heart = 100%)				% (Trans- verse Diameter of Smaller Heart = 100%)
				Cm.	Cm.	Cm.		Cm.	Cm.	Cm.	
Decrease of 20% or more...	19	6.7	187	29.5	28.9	-0.6	-2.2	15.3	12.3	-3.0	-24.4
Decrease of 10.0-19.9%...	106	37.1	114	29.2	29.1	-0.1	-0.3	14.5	12.7	-1.8	-14.2
Decrease of 0-9.9%.....	146	51.0	112	28.6	28.4	-0.2	-0.7	13.8	13.0	-0.8	-6.2
Increase of 0-8.0%.....	15	5.2	184	27.5	27.8	+0.3	+0.8	13.1	13.5	+0.4	+2.6
Total.....	286	100	122	28.8	28.6	-0.2	-0.7	14.2	12.9	-1.3	-10.1

TABLE XIX

CHANGES IN THE ANGLE OF THE ELECTRICAL AXIS IN 292
PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE AFTER
RICE DIET

No. of Patients	Per- cent age	Angle of Electrical Axis (Degrees)				Period on Rice Diet (Av.) Months
		Range of Change	Before Rice Diet	After Rice Diet	Change (Average)	
1	2	More than -25	-10	-55	-45	2
6		-15 to -25	+19	0	-19	4
173	60	±14	+13	+17	+4	6
70	38	+15 to +25	+13	+32	+19	7
42		More than +25	+6	+43	+37	8

length of time the diet was followed is evident from Figures 3 to 6 and Table xvi.

In 125 of the 500 patients (forty with and eighty-five without evidence of renal involvement) the blood pressure figures returned to normal or almost normal values (below 145/95 mm.). The blood pressure of these patients before the rice diet ranged from 222/148 to 158/98, average 181/107 mm.; the average pressure after four to 898 days, average ninety-four days, of rice diet was 132/85 mm. Seven patients are

TABLE XX

CHANGES OF T₁ IN 310 PATIENTS
WITH HYPERTENSIVE VASCULAR DISEASE AFTER RICE DIET

No. of Patients	T ₁ Before Rice Diet	T ₁ After Rice Diet	Period on Rice Diet (Average) Months
Change in Direction to Inverted			
2	diphasic	inverted	3
1	upright	diphasic	6
3	low upright	diphasic	4
1	upright	low upright	2
No Change			
52	inverted	inverted	5
21	diphasic	diphasic	4
5	low upright	low upright	2
136	upright	upright	6
Change in Direction to Upright			
19	low upright	upright	5
4	diphasic	low upright	7
19	diphasic	upright	8
17	inverted	diphasic	7
5	inverted	low upright	7
25	inverted	upright	10

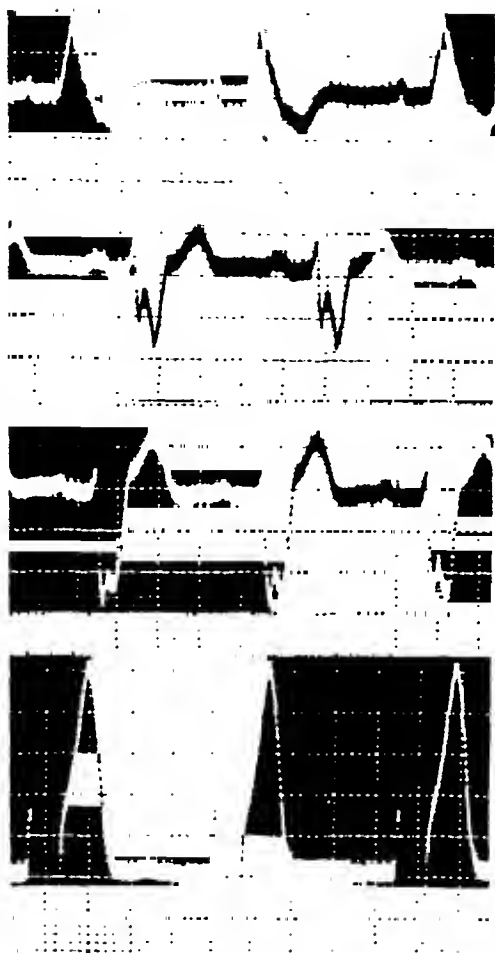


FIG. 19. P. K., a male, fifty-six, had left bundle branch block. The EKG did not change. (See also Fig. 18.)

included in this group whose "mean" arterial pressure dropped less than 20 mm. Hg and who therefore are counted as "not improved" in the previous paragraphs and tables.

The changes in diastolic pressure are analyzed separately in Table xvii.

Of 406 patients whose initial diastolic pressure was 100 mm. Hg or more 388, i.e., 96 per cent, had a decrease of 1 to 62 mm., average 18 mm., whereas only eighteen patients, i.e., 4 per cent, had an increase of 1 to 22, average 7 mm.

It has been assumed that the lowest blood pressure figure obtained after 0.6 Gm. sodium amytal indicates the maximum decrease which could be expected in the

individual patient from any form of treatment. Figure 7 shows in three typical charts that the blood pressure values obtained without sodium amytal after rice diet may be far lower than the lowest values reached during the sodium amytal test before the diet.

Heart Size. The assumption that cardiac enlargement in hypertensive vascular disease is desirable in order to overcome the increased peripheral resistance has been a pious self-deception of the physician who had no means of influencing the disease and preventing the progressive cardiac breakdown.

Cardiac enlargement in hypertensive vascular disease has been found to disappear when the patient is given the rice diet. Chest films taken before and after rice diet show decreases in the heart sizes with changes in the transverse diameter up to 30 per cent. Decrease in heart size does not necessarily coincide with decrease in blood pressure. In a number of patients whose blood pressure remained at a constant high level or showed only an insignificant reduction, a considerable decrease in heart size was found. (Figs. 14 and 15.)

Six foot chest films of 286 patients taken before and after one month or more of dietary treatment (no digitalis or other drugs) are available for comparison. Table xviii combines the averages of the measurements of the transverse diameter of the heart and of the chest diameter grouped according to the extent of change.

Before the rice diet the transverse diameters of the hearts of the 286 patients ranged from 10.2 to 19.4 cm.; the average was 14.2 cm. After the rice diet they ranged from 9.4 to 18.2 cm.; the average was 12.9 cm.

In 15 of the 286 patients (5 per cent) the heart became larger. In these patients the transverse diameter of the heart showed an average increase of 2.6 per cent. The chest diameter (average) increased by 0.8 per cent. The average period on the diet was

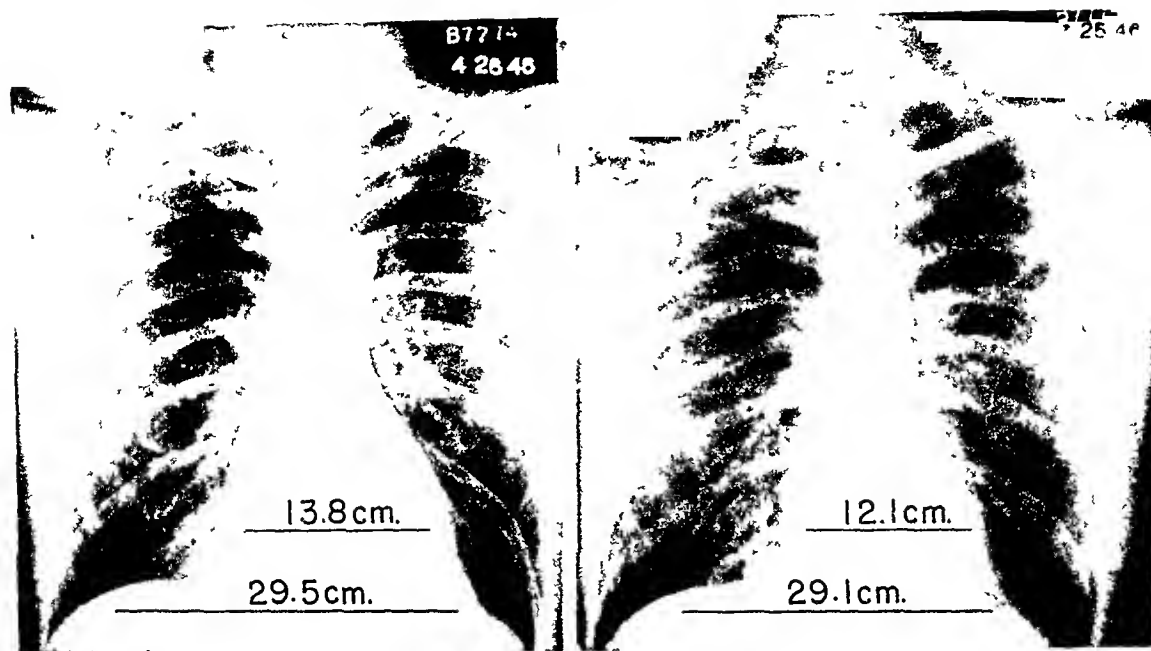


FIG. 20. A and B, C. O. a male, forty-three years of age, had hypertensive vascular disease of ten years' duration, left bundle branch block and dyspnea. Total PSP excretion in two hours, 57 per cent. Rice diet was started May 4, 1946, and strictly followed (10–11 mg. Cl per 100 cc. of urine). No medication was given. The patient became asymptomatic. There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 14 per cent. (Fig. 21.)

184 days. The average heart size in this group before treatment was the smallest found.

In 271 of the 286 patients (95 per cent) the heart became smaller with an average change in the transverse diameter of 10.6 per cent. The chest diameter decreased by 0.6 per cent (average). The average period on the diet was 118 days.

Figures 8 to 15, 17, 18, 20 show typical changes in the heart picture produced by the rice diet.

Electrocardiograms. The blood supply to the heart muscle will be inadequate whenever the coronary blood flow is decreased without a simultaneous decrease in the myocardial energy requirements, or whenever the myocardial energy requirements are increased without a simultaneous increase in the blood supply through the coronaries. In either case the effects of the deficiency in oxygen and nutrient substances, with the resulting chemical changes and consequent clinical manifestations, are easily predictable.^{7,28} The natural course

of these events is recorded by the electrocardiographic findings which indicate advancing myocardial impairment: left axis deviation, T_1 inversion, arrhythmias, conduction defects or myocardial infarction.

An attitude of resignation has prevailed with regard to the abnormal electrocardiogram in hypertensive heart disease. "It is a pertinent feature of records denoting left ventricular strain that the changes are slow in their evolution and more or less permanent once they have appeared."²⁹ "When once established the T-wave and the RS-T defects described persist and remain unaltered until the death of the patient."³⁰

Electrical axis and T_1 waves were studied in the electrocardiograms of 310 patients with hypertensive vascular disease before and after the rice diet. None of these patients received digitalis or any other drug. All electrocardiograms were made with the patient at rest in a recumbent position. The period between the two electrocardiograms compared was one month to thirty-three months, an average of six months. In 18

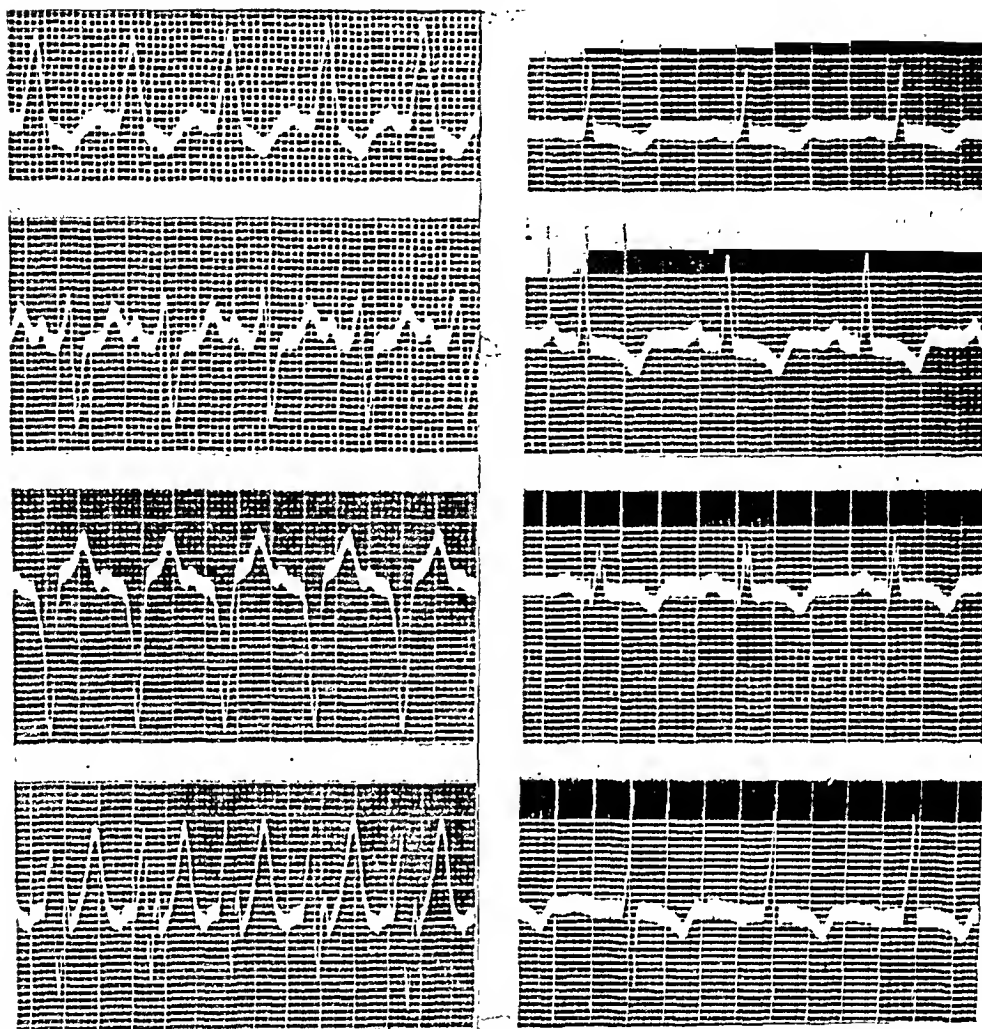


FIG. 21. C. O., a male, forty-three years of age, had hypertensive vascular disease of ten years' duration and dyspnea. April 29 to May 8, 1946: blood pressure, average, 179/126; total PSP excretion in two hours, 57 per cent. Rice diet was started May 4, 1946, and strictly followed (10–11 mg. Cl per 100 cc. of urine). No medication was given. July 24 to July 25, 1946: blood pressure, average, 157/110. The patient became asymptomatic and there was disappearance of left bundle branch block. (Fig. 20.)

of the 310 patients the electrical axis could not be evaluated. In the remaining 292 patients the angles of the electrical axis were:

	Before Diet	After Diet
More than +30 degrees	in 89 patients	in 131 patients
0 to +30 degrees	in 97 patients	in 91 patients
Less than 0 degrees	in 106 patients	in 70 patients

The changes in the angle of the electrical axis of these patients are summarized in Table xix.

Of the 119 patients whose electrical axis changed more than $\pm 14^\circ$ during the treatment 7, i.e., 6 per cent, showed a decrease; 112, i.e., 94 per cent, showed an increase in the angle of the electrical axis.

The T waves in lead I were evaluated in 310 patients. Before the rice diet was started T_1 was normally upright or low upright in 165, diphasic or inverted in 145 patients. The changes during the treatment are shown in Table xx.

In seven patients there was a change of T_1 in the direction from upright to inverted. In 89 patients there was a change of T_1 in the direction from inverted to upright. In

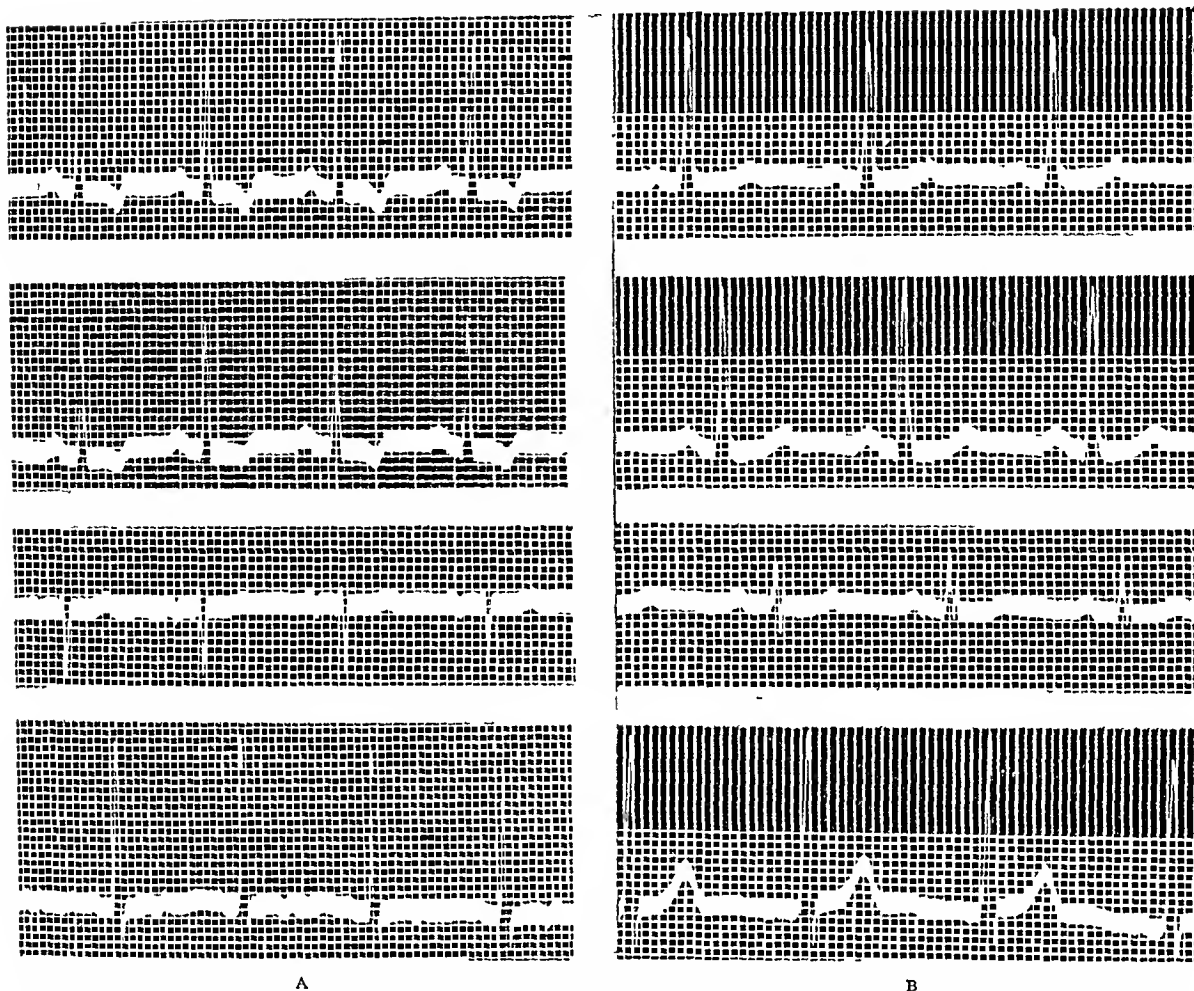


FIG. 22. A and B, R. L., a male, twenty-three years of age, had hypertensive vascular disease of three years' duration with advanced retinopathy; total PSP excretion in two hours: 2.5 per cent. No digitalis was given. Rice diet was started on December 18, 1945. Blood pressure, average, December, 18 to December 24, 1945: 222/148; January, 15 to January 21, 1946: 153/112. March, 11 to March 22, 1946: 134/94. Inverted T_1 became upright within one month. The lowest blood pressure was reached two months later. (Figs. 3 and 30.)

ninety-nine patients the T_1 waves were completely inverted before treatment. In thirty of these ninety-nine patients T_1 became upright with the diet. In no patient did the reverse occur.

Excluding the patients who at the start of the rice diet already had an inverted T_1 (and in whom there could be no further change for the worse according to the grouping of Table xx), the percentage of those changing for the worse during the rice diet was three. Excluding the patients who at the start of the diet already had an upright T_1 (and in whom there could be no further improvement according to the grouping of Table xx), the percentage of those changing for the better was fifty-two.

The shortest time in which an inverted T_1 became normally upright was one month. (Fig. 22.) The average was ten months. In the patient whose EKG is shown in Figure 23 it took three years.

Of the 292 patients in whom it was possible to evaluate the changes both in electrical axis and in T_1 , eighty-seven patients (30 per cent) had an initial electrical axis above $+10^\circ$ and an upright T_1 . Of these eighty-seven patients 7 (8 per cent) showed a change for the worse in that the electrical axis decreased below $+10^\circ$ and/or T_1 became diphasic; 80 (92 per cent) did not change with the rice diet.

Of the 292 patients 205 (70 per cent) had an initial electrical axis below $+10^\circ$ and/or

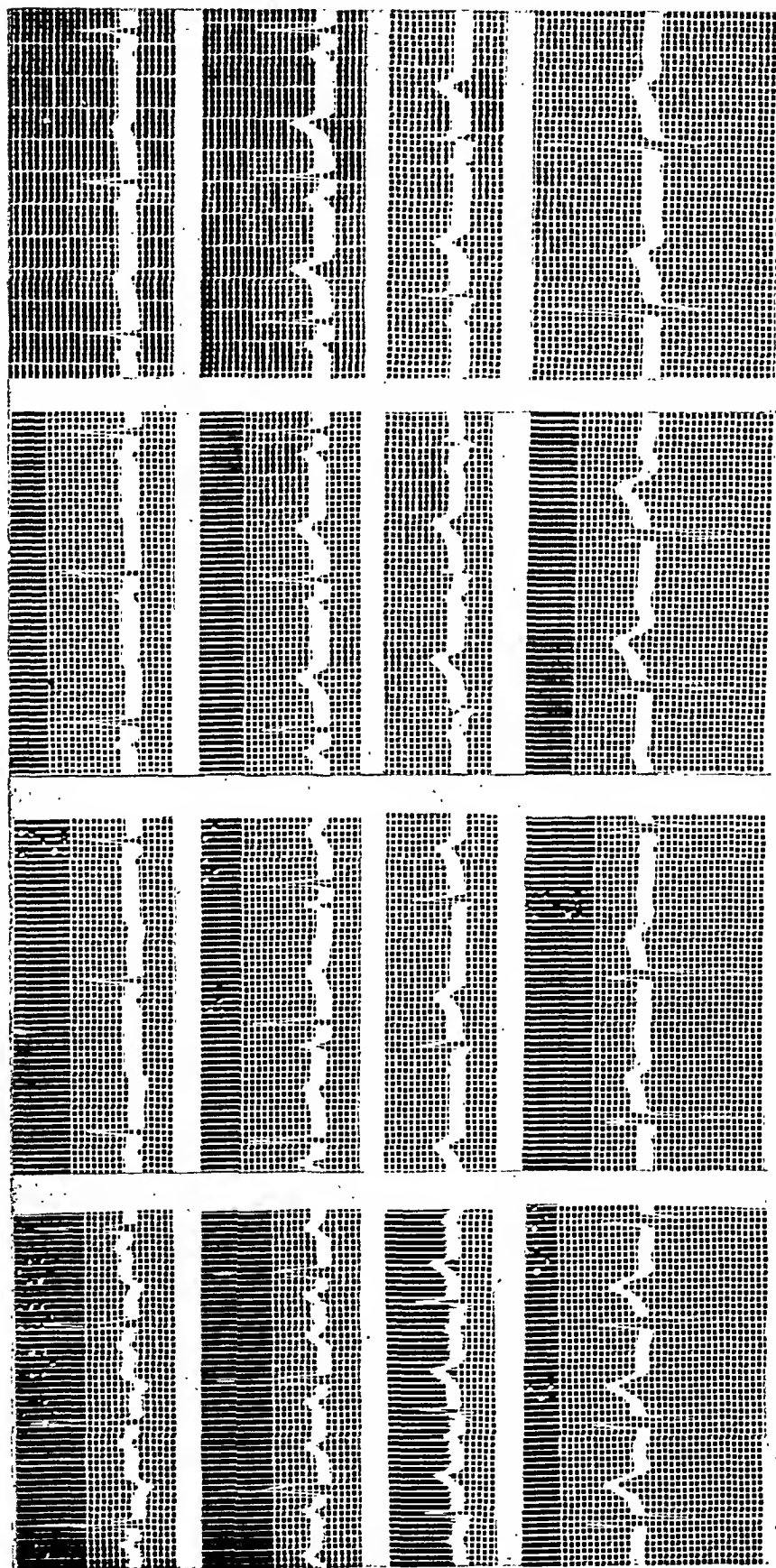


FIG. 23. A. [E. H., female, thirty-six years of age, had hypertensive vascular disease of one year's duration. Chronic pyelonephritis was present. There were severe headaches and retinal hemorrhages and "silver wire arterioles." Previous treatment with salt-poor diet; no digitalis was given. Total PSP excretion in two hours: 9-25 per cent. Rice diet was started April 13, 1943: it was moderately well followed. No medication was given. Patient was asymptomatic and working. Blood pressure averages: April 5 to April 26, 1943: 223/149; March 8 to March 10, 1944: 116/92; Feb. 20 to March 3, 1945: 159/109; May 23 to May 29, 1946; 118/79. Inverted T_1 has become normally upright three years after decrease of blood pressure.

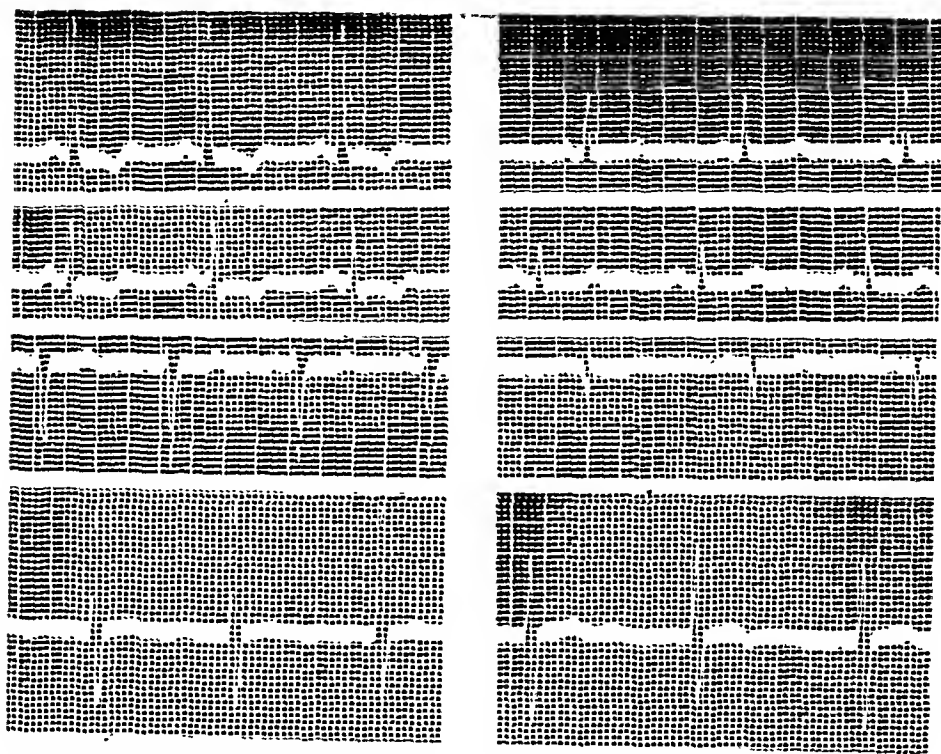


FIG. 24. A and B, C. G., a male, forty-nine years of age, had hypertensive vascular disease of two years' duration with severe headache. Two strokes occurred in 1944. He was treated with sedatives; was given no digitalis; April 6 to April 22, 1945: blood pressure average, was 196/105; total PSP excretion in two hours: 48 per cent. Rice diet was started April 24, 1945: it was followed strictly (5–20 mg. Cl per 100 cc. of urine). October 8 to October 11, 1945: blood pressure average was 136/80. There was a decrease in the blood pressure and an increase in the angle of electrical axis. Inverted T_1 became upright.

a diphasic or inverted T_1 . Of these 205 patients 119 (58 per cent) remained unchanged; eighty-six patients (42 per cent) showed an increase in the electrical axis to more than $+10^\circ$ and/or a change of T_1 from diphasic or inverted to upright.

Retinopathy. Advanced retinopathy with papilledema, hemorrhages or exudates is a danger signal in hypertensive vascular disease. "Hemorrhages associated with white spots in the retina (hypertensive neuroretinopathy) are ominous signs. Death commonly follows within a year."³¹

Vascular retinopathy has been found to disappear with the rice diet. The retinal improvement does not necessarily coincide with decrease in blood pressure. Very severe retinopathy has disappeared in patients when the blood pressure remained at a constant high level or showed only an insignificant reduction. (Figs. 27 to 29.)

Papilledema, hemorrhages or exudates, frequently in combination, were present in 140 of the 500 patients. In eighty-eight of these, eyeground photographs taken both before and after the rice diet (one to thirty months) are available for comparison. Papilledema was found in twenty-three of the eighty-eight patients. In seventeen it disappeared completely, in five partially and in one remained unchanged. Hemorrhages were found in fifty-five of the eighty-eight patients. In thirty-nine they disappeared completely, in fifteen partially and in one remained unchanged. Exudates were found in seventy of the eighty-eight patients. In forty-two they disappeared completely, in twenty-three partially and in five remained unchanged. In one of the patients in whom the exudates cleared up partially small hemorrhages occurred after a period of twelve

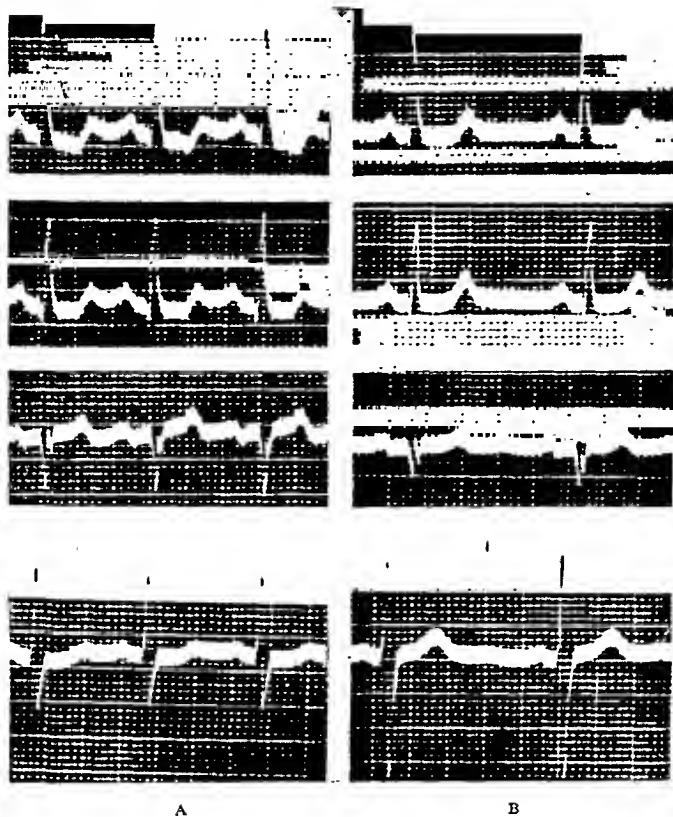


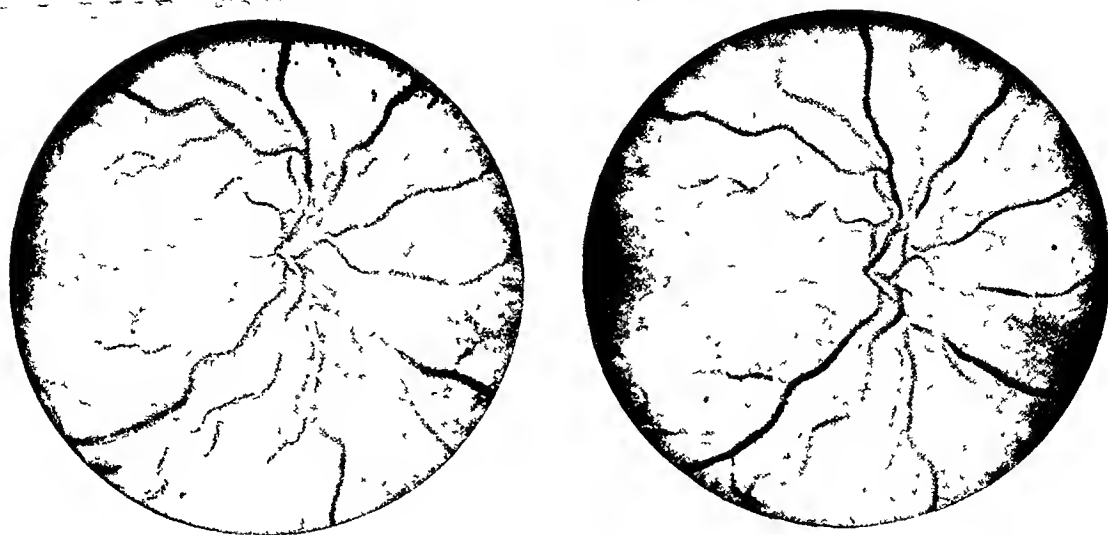
FIG. 25, A and B, F. G., a female, fifty-two years of age, had hypertensive vascular disease of twelve years' duration which began in toxemia of pregnancy. There were severe headaches. She had a stroke in May, 1946. She had previous treatment in a hospital with bedrest and a reduction diet. She had been given sedatives for the last three years. No digitalis was given. August 8, 1946; blood pressure was 238/128; total PSP excretion in two hours: 57 per cent. Rice diet was started August 10, 1946; it was strictly followed for six weeks (5 mg. Cl per 100 cc. of urine). September 20, 1946 to September 26, 1946: blood pressure, average, was 150/100. There was a decrease in blood pressure. The diphasic T_1 has become upright.

months on the diet (which had not been strictly followed).

Those patients in whom the retinopathy remained unchanged had been on the diet from one to three and one-half months except for one patient with exudative stippling who was on the rice diet for nineteen months. The patients in whom the

retinopathy cleared up only partially had been on the rice diet from one to seventeen months, an average of five months. The period of time in which the retinal changes disappeared completely ranged from two to thirty months, an average of fourteen months.

Figures 26 to 30 show typical eyeground photographs before and after the diet.



A

B

FIG. 26. A and B, D. L., a male, fifty-four years of age, had hypertensive vascular disease of at least six months' duration. His previous treatment consisted of low-fat, low-protein diet and sedatives. April 19, 1946 to May 6, 1946, blood pressure average was 221/144; EKG T_1 inverted; total PSP excretion in two hours: 35 per cent. Rice diet was started April 26, 1946, it was strictly followed (5-13 mg. Cl per 100 cc. of urine). March 25 to March 26, 1947 Blood pressure, average, was 177/112, EKG T_1 was upright. September 22 to September 24, 1947, blood pressure, average, was 149/106; EKG T_1 upright. There was a disappearance of papilledema and exudates before lowest blood pressure level was reached.



A

B

FIG. 27. A and B, W. A., a male, thirty-two years of age, had hypertensive vascular disease of eighteen years' duration. Sympathectomy was performed in the Mayo Clinic in 1945. Since July, 1946, there had been progressive impairment of vision in the left eye. February 19 to February 21, 1947: blood pressure average was 255/158; total PSP excretion in two hours: 40 per cent. Rice diet was started February 21, 1947; it was moderately well followed (12-51 mg. Cl per 100 cc. of urine). September 22 to September 26, 1947 blood pressure, average 230/138. There was marked improvement of vision. There was a disappearance of papilledema, almost complete disappearance of hemorrhages and exudates in spite of persistence of high blood pressure.

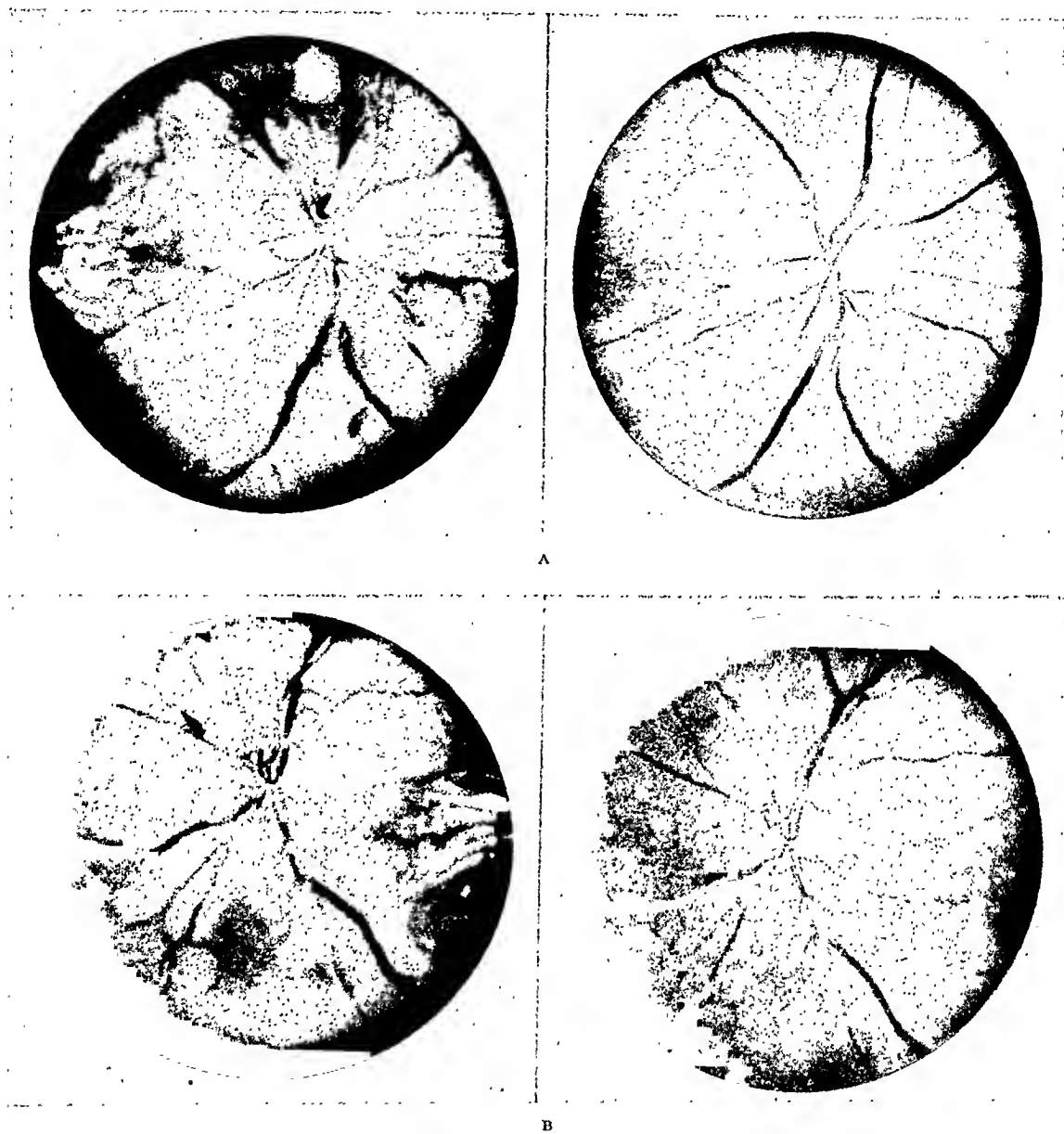
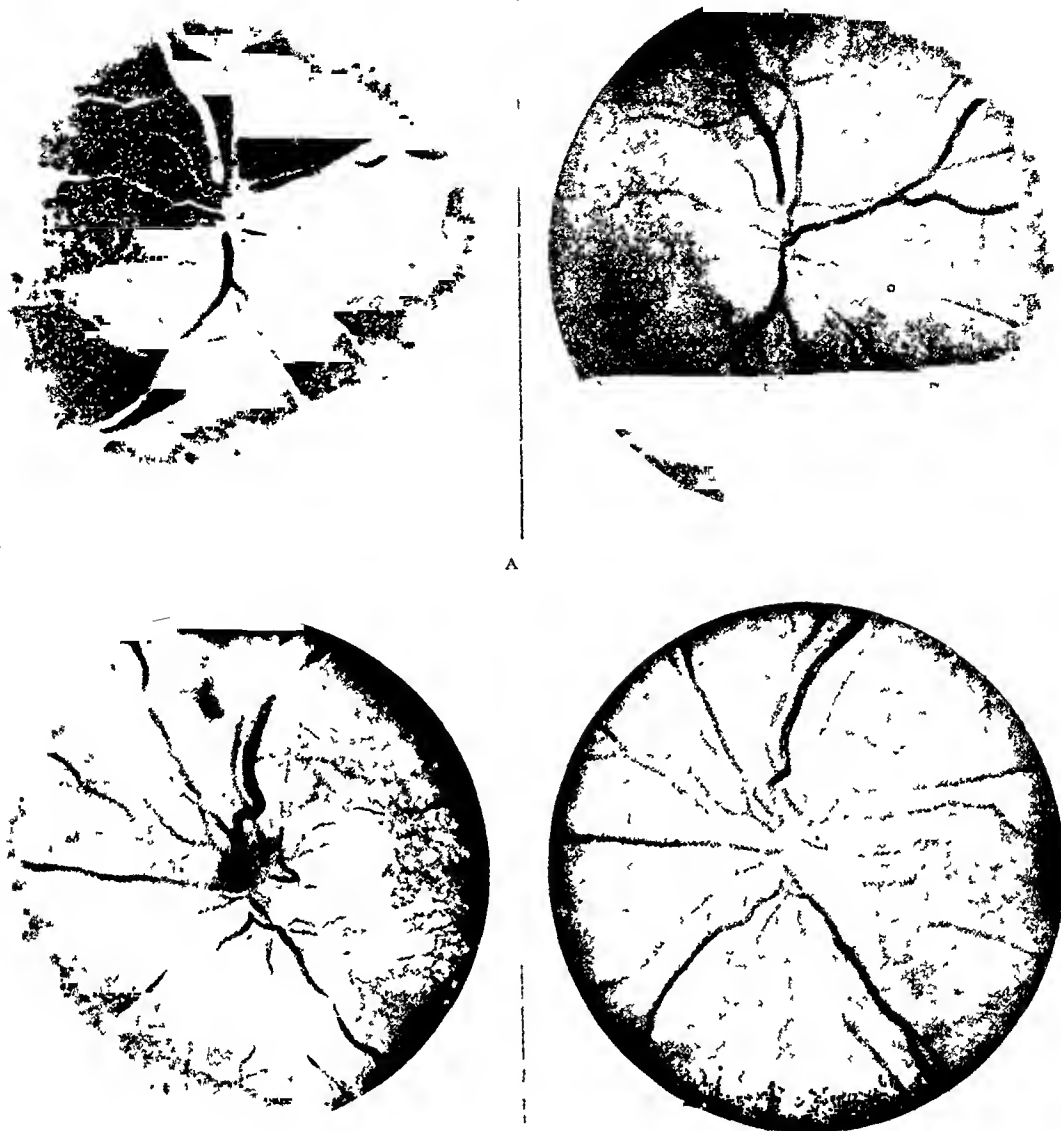


FIG. 28. A and B, L. W., a female, forty-five years of age, had hypertensive vascular discase of at least four months' duration. July 16 to August 5, 1944: blood pressure, average, 225/153; total PSP excretion in two hours, 59 per cent. Rice diet was started July 23, 1944 and strictly followed (4-24 mg. Cl per 100 cc. of urine). August 8 to August 13, 1945: blood pressure, average, 215/138. There was a disappearance of papilledema, hemorrhages and exudates in spite of persistence of high blood pressure.



B

FIG. 29. A and B, A. McA., a male, thirty-eight years of age, had hypertensive vascular disease of at least one year's duration. He was previously treated with sedatives and low-salt diet. December 8 to 20, 1945: blood pressure, average, 216/132; EKG T_1 inverted, total PSP excretion in two hours, 58 per cent. Rice diet was started, December 13, 1945 but was not strictly followed (28–55 mg. Cl per 100 cc. of urine). May 5 to 8, 1947. blood pressure, average, 208/123; EKG T_1 upright ————— Papilledema, hemorrhages, exudates disappeared in spite of persistence of high blood pressure.

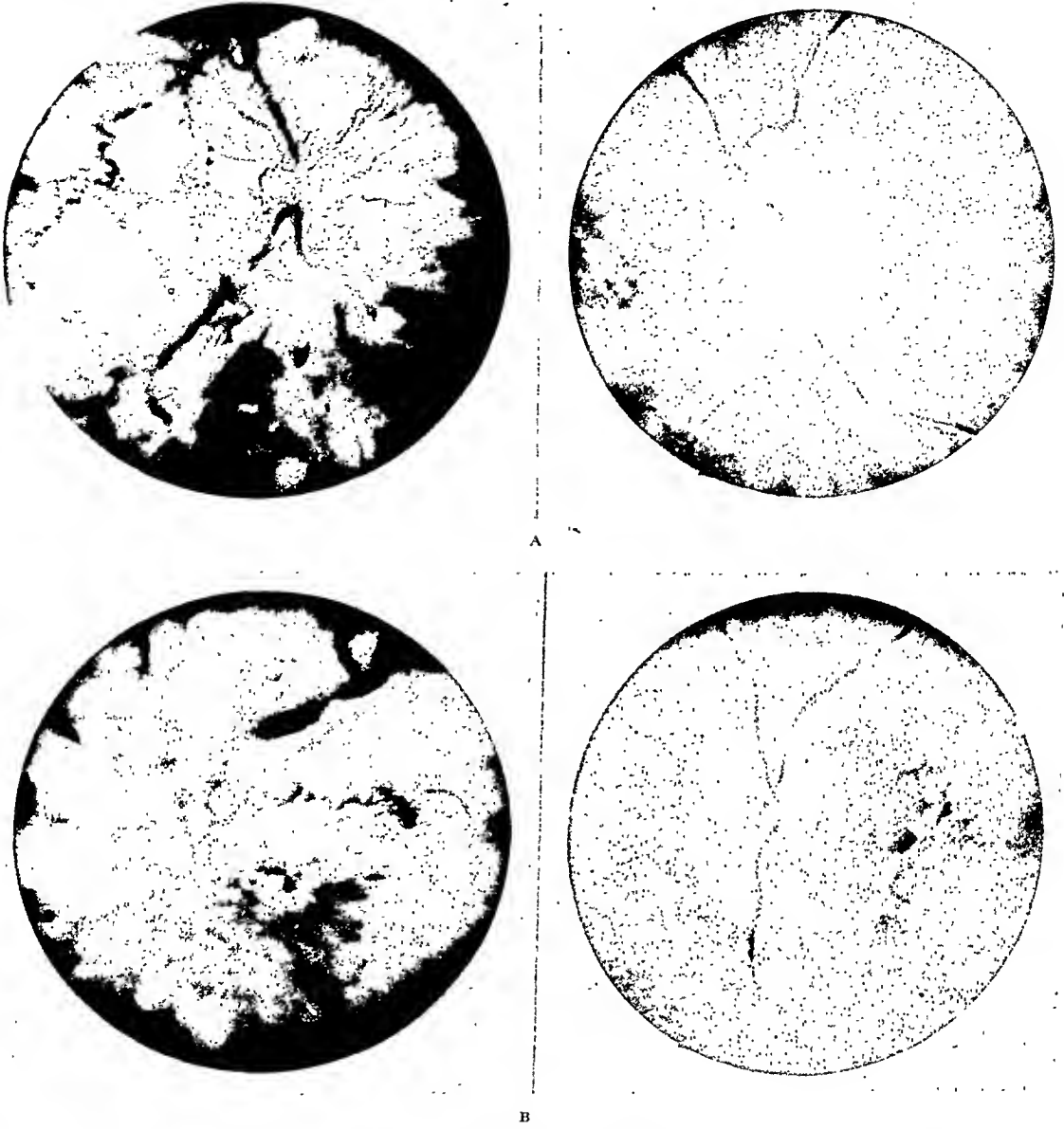


FIG. 30. A and B, R. L., a male, twenty-three years of age, had hypertensive vascular disease of three years' duration. Previous treatment consisted of a "modified rice diet." December 18 to December 24, 1945: blood pressure, average, 222/148; EKG T_1 inverted; total PSP excretion in two hours, 2.5 per cent; NPN 79 mg. per 100 cc. blood; cholesterol 340 mg. per 100 cc. serum. Rice diet was started December 18, 1945 and strictly followed for three months (8–21 mg. Cl per 100 cc. of urine). March 11 to 22, 1946: blood pressure, average 134/94; EKG T_1 upright. After March, diet was poorly followed (192–255 mg. Cl per 100 cc. of urine). August 15 to 21, 1946 and October 2 to 5, 1946: blood pressure, average, 194/133; EKG T_1 upright; NPN 60 mg. per 100 cc. blood; cholesterol 173 mg. per 100 cc. serum. There was a disappearance of papilledema, hemorrhages, exudates and no recurrence of retinopathy although diet was broken and hypertension recurred.

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Low Salt Diets and Arterial Hypertension*

HENRY A. SCHROEDER, M.D.

St. Louis, Missouri

IT is difficult to discuss the effect of diets low in salt upon the blood pressure and subsequent course of patients suffering from arterial hypertension of unknown cause without first examining the condition itself and its fundamental nature. So little is known of its etiology and mechanism that the attitude one adopts becomes a matter of belief based on the scant evidence available. One idea is that etiologic factors in all cases of arterial hypertension are the same; that similar interacting influences, or disturbances, lead to an altered vascular physiology expressed by hypertension. This view is untenable. Four simple mechanical factors act to maintain a normal blood pressure as well as a high one; i.e., the volume of blood, its viscosity, the function of the heart and the resistance to blood flow in the periphery. Many others affecting not only the cardiovascular system, but general and apparently unassociated bodily functions, may express their actions by changes in blood pressure. In fact, the blood pressure can be considered as a resultant of a number of interacting influences, and can become decompensated in a number of ways. Some of these are well understood but many are not. It may be as untrue to state that all cases of arterial hypertension have the same basic disturbance as it is to state that all patients with fever have the same etiologic agent.

Another theory is that patients with pathologic conditions associated with hypertension, and to which hypertension is considered secondary, may have different etiologies and mechanisms depending upon the disease present. All other patients with conditions not associated with these known diseases are considered to have "essential"

hypertension. A similar etiology and mechanism is, therefore, postulated for such subjects. This is the prevailing viewpoint at present. With this theory goes a tacit assumption that diagnostic methods are accurate enough to differentiate obscure underlying conditions. The mechanism of the elevation of blood pressure of most patients in this category may well be a uniform one, but the assumption of a common etiology cannot be made at this time.

The third point of view, so aptly expressed by Fishberg,¹ is that so-called "essential" hypertension is a "collective concept for a number of conditions having in common the positive characteristic of arterial hypertension and the negative one of the absence of primary renal disease." On this theory, it becomes possible to consider that a number of different pathologic conditions are being grouped as a syndrome in which various disturbances lead to elevation of the blood pressure with its concomitant cardiovascular and renal changes. Furthermore, when therapeutic results are obtained in some individuals but not in all, one can examine them according to their actions on these different disturbances and not accept or discard them in the light of one mechanism only. In the following discussion, the possibility that we are dealing with several different conditions having a common clinical finding should be borne in mind.

SODIUM CHLORIDE AND ARTERIAL HYPERTENSION

Any relationship which may exist between salt (sodium, chloride or both) and arterial hypertension is a complex one. To break it down into its component parts, one

* From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine, and Barnes Hospital, St. Louis, Missouri, under a grant-in-aid from the U. S. Public Health Service.

must consider the various interacting influences which may be at work. The question of whether or not there is a disturbance of sodium chloride balance in hypertension can only be answered by examining ways in which such a disturbance could act, for the evidence on this point is far from clear.

The kidneys are the first organs to be considered. Is there a specific retention of sodium chloride by hypertensive kidneys? Little is known of the effect on these ions of mild renal vascular disease or constriction. In right-sided heart failure, for example, the clearance and the excretion of salt are reduced.^{2,3} In hypertension Ambard and Beaujard⁴ postulated a "dry retention" of salt and advocated for the first time a salt-poor diet to counteract it. Later, Ambard abandoned this idea, but many others continued to entertain it. Recently, with the present revival of interest in the subject, Perera⁵ showed that hypertensive patients placed on twenty-four hours of rigid salt restriction did not lose weight or water, while normal individuals did. Both groups lost the same amount of salt, but in two pairs of subjects the clearance of sodium chloride was reduced in the hypertensives. Farnsworth,⁶ on the other hand, studying the renal excretion of chloride, found that chloride clearances were increased in hypertensive patients and that the renal tubules demonstrated a specific failure to reabsorb this ion. Furthermore, Selye⁷ recently reported that some hypertensive patients with high diastolic pressures showed an increase in blood sodium relative to chloride. She believes that this is the result of the action of the adrenal cortex. These findings do not support Ambard's original idea of "retention chlorurée sèche."

If there has not been demonstrated a specific renal diminution of salt excretion, one must examine those factors which can influence the kidney to retain salt and relate their activities to what is known about hypertension. Among them are: (1) the relation of the adrenals to salt balance; (2) the relation of the adrenals to hypertension; (3) the relation of other influences

to the adrenals and (4) the relation of salt to hypertension.

Salt and the Adrenal. The relation of sodium chloride balance to the adrenal cortex is well known. Steroid compounds similar to those of the adrenal are specific for counteracting the derangements in sodium balance found in adrenal insufficiency. The loss of sodium chloride in Addison's disease is the predominant, though not the only, disturbance which accounts for the symptoms and findings. Disturbances of electrolytes do occur in some cases of adrenal cortical hyperfunction, with increases in the blood levels of sodium and decreases in potassium.^{8a} Rats reared on a low sodium diet excrete radioactive sodium more rapidly than normal rats,^{8b} and a diet free of sodium has been said to produce changes in the adrenals.^{8c} The action of the adrenal cortex and of desoxycorticosterone on salt balance is thus an established fact, although there are still many important questions to be answered concerning its method of acting and its relation to other organs and systems.

Adrenal Cortical Factor in Hypertension. Any discussion of the rôle of sodium chloride in arterial hypertension must involve the part the adrenal glands play in this condition. About this there is considerable controversy. Evidence for an adrenal factor, and particularly an adrenal cortical factor, in arterial hypertension is suggestive but not thoroughly convincing. It is obvious that the adrenal cortex is necessary for maintenance of an elevated blood pressure. It is also necessary for maintenance of a normal blood pressure. Bilateral adrenalectomy will prevent the development of experimental hypertension and lower the blood pressure in one already established unless substitution therapy is used. But other conditions, sometimes disregarded, are just as necessary as mentioned previously. Even a normal body temperature may be required, for an elevated blood pressure may fall during bouts of fever induced by disease or by the introduction of pyrogens.⁹

A conclusion that the adrenal cortex is necessary for hypertension to be established does not necessarily implicate this organ as being primarily involved. In some cases it may be, however. Hypertension, associated with Cushing's syndrome, can apparently result from tumors or hyperplasia of the adrenal cortex. In this condition one is drawn to the conclusion that an adrenal mechanism plays a primary or initiating rôle. Small adenomas of the adrenal cortex have been described in about 1.45 per cent of all autopsies; patients showing these tumors frequently exhibited hypertension in life.¹⁰ Hyperplasia of the cortex, associated with hypertension, has also been described.¹¹ These findings have been doubted.¹² It is possible that these cases represent a different type of the condition, although so far no attempt has been made to classify them accurately on clinical grounds. Heinbecker,¹³ however, believes that an adrenal-pituitary-renal relationship is disturbed in arterial hypertension, resulting in pituitary changes and renal ischemia.

Measurements of the urinary excretion of cortical-like and other steroids have not offered proof that these substances are abnormal in cases of hypertension even if values are low.¹² Total amounts of 17-ketosteroids or other steroid metabolites may give misleading information concerning the activity of the adrenal cortex, unless the values found are well outside the normal (and fairly wide) range. All cortical steroids and their metabolites are not measured by this method. If there is any suggestion to be gained from such studies, it is that the cortex may be underactive.

More direct and exact measurements of these substances have yielded interesting evidence that some disturbance of the adrenal cortex or of the body's ability to metabolize steroids may be present in some cases of hypertension. Recently, Dobriner¹⁴ reported the presence of a metabolite of adrenal cortical steroids Δ^9 , etiocholenalone, in the urine of half of six patients with hypertension. These were all women. It was also present in two normal subjects, one

male and one female, out of twenty-eight and in twenty-five of twenty-six patients with carcinoma, excluding that of the breast. It was present in five of seven subjects with Cushing's syndrome as well. Another so far unidentified metabolite occurred in the urine of all of five hypertensive women and in only two of nine normal subjects. These findings suggest that alterations in the metabolism of adrenal cortical steroids occur in some cases of arterial hypertension and Cushing's syndrome. Dobriner's careful analyses, and time-consuming methods of extraction and identification of minute quantities of steroids from large volumes of urine are inapplicable to the usual research laboratory. It is hoped that more rapid and simple methods for the study of these compounds may be developed in order that they be correlated further with special varieties of hypertension and other diseases.

Goldblatt,¹⁵ in his recent excellent review, states, "Of the endocrine organs, the only one that may possibly play a significant, even if only a secondary part (in hypertension) is the adrenal, although this conclusion is contested on basis of inadequate evidence." Newer evidence does not yet controvert this viewpoint. Until the disease with its secondary manifestations can be consistently reproduced by disturbing adrenal function, evidence that the adrenals are implicated as primary etiologic agents in most patients must be considered inadequate. If they are concerned, it is uncertain whether their secretions are increased or diminished.

Relation of Salt and Desoxycorticosterone Acetate to Hypertension. The relation of salt to hypertension is a matter of controversy. Most of the evidence for salt being important comes from studies on patients using low salt diets which will be discussed later. There is accumulating evidence, however, that at least under some conditions sodium chloride, taken in large amounts, may adversely affect the blood pressure of hypertensive patients more than of normal ones. A high salt intake may reverse the hypoten-

sive action of low salt diets.¹⁶ The treatment of Addison's disease by desoxycorticosterone acetate and salt is often accompanied by a rise in blood pressure to levels over 140 mm. Hg systolic and 90 diastolic, sometimes reaching diastolic levels of 100 to 110.^{17,18} When desoxycorticosterone acetate and salt were given to normal subjects a small but significant rise in blood pressure occurred after two to three weeks. When the same amounts were given to patients with hypertension, the blood pressure became higher in one to four days.¹⁹

Experimentally, the blood pressure of rats and dogs can be elevated by the administration of salt and desoxycorticosterone acetate, and renal vascular lesions have been reported to occur.²⁰ That desoxycorticosterone acetate and salt will elevate blood pressure appears to be an established fact, not only in animals, but in human beings as well. The administration of large amounts of salt alone, however, to normal subjects, does not change blood pressure.²¹ Plasma volume and venous pressure may, in some cases, become considerably elevated after salt, with extracellular water, measured by "thiocyanate space" increased and much sodium retained.

Landis²² recently reported some interesting observations on hypertensive rats. Choices of sodium chloride and other electrolytes were offered to three groups of animals: normal, moderately hypertensive and severely hypertensive. Those exhibiting moderate hypertension ingested significantly less salt than did the other groups. One implication of these results is that there may be some dysfunction of certain functions of the adrenal in these animals.

These experiments do not incontrovertibly support the idea that the adrenal cortex is disturbed in hypertension. They merely show that experimental alterations in salt balance may affect blood pressure when desoxycorticosterone acetate is used. These results have not been duplicated by the administration of whole cortical extract.⁸ Furthermore, the adrenalectomized animal and human being seem to be more sus-

ceptible to the hypertensive actions of these substances than are normal ones. This has led Soffer²³ to suggest two vascular regulating factors of opposite action in the adrenal cortex which may be disturbed in hypertension and which are present in whole gland extracts. One of these may be similar to desoxycorticosterone acetate. The other may be diminished in hypertension and absent after adrenalectomy. If desoxycorticosterone acetate can act as a pressor or vasoconstrictor substance, this would be important in some cases of hypertension.*

Relation of Other Influences to the Adrenals and Kidneys. It is not within the province of this discussion to consider the complex interrelations between the adrenal cortex and other endocrine organs. There are three influences, however, which should be mentioned. The first concerns the work of Marshall and Kolls²³ who found that in dogs extirpation of one adrenal resulted in markedly increased excretion of chloride and water by the homolateral kidney, while the excretion of creatinine was unaffected. This suggested that the change was independent of renal blood flow. The same effect was observed after unilateral section of the splanchnic nerve and Marshall concluded that the results were due to nervous influences. It is probably impossible to remove a dog's adrenal without severing many of the sympathetic nerves which lie in a plexus about the gland and thus partially denervating the kidney. These experiments suggest the presence of a nervous (or hormonal) influence on the renal excretion of chloride which is not humoral. The converse, i.e., that stimulation of sympathetic nerves leads to salt retention, has not been demonstrated.

The second influence concerns the recent demonstration by Vogt²⁴ directly and by

* Since this manuscript was prepared, desoxycorticosterone acetate has been found to elevate the blood pressure of hypertensive patients when it is injected intravenously. It does not change the blood pressure of normal individuals. Similar compounds, i.e., progesterone, dehydroisoandrosterone acetate, Δ^5 pregnenolone, testosterone and whole adrenal cortical extract (Upjohn) did not significantly affect blood pressure.²⁷

Long²⁵ indirectly that epinephrine is a potent stimulus to adrenal cortical secretion. Of great interest to this problem is the finding that "stimulation of the sympathetic nervous system and consequent liberation of epinephrine is capable of increasing

ure as did Volhard.²⁷ Other investigators have obtained effects with this diet and various theories have been proposed to account for them, while many others were not convinced of its efficacy. Diets of this type came into rather wide use in Europe

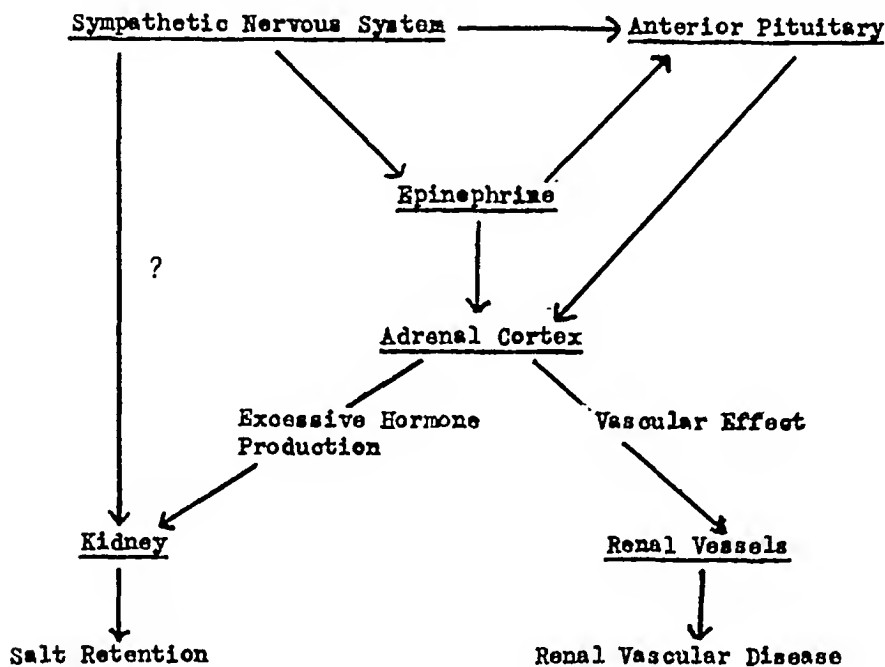


FIG. 1. Possible influences on the renal retention of sodium chloride.

cortical hormone output."²⁵ If hyperactivity of the sympathetic nervous system can cause the adrenal cortex to liberate salt-retaining hormone, which has not yet been shown, a mechanism is provided for salt retention in hypertension. There seems to be evidence that overactivity of the sympathetic nervous system may play a part in some cases of "essential" hypertension, although perhaps not in all.

If one were to attempt to diagram these influences in order to clarify them, a scheme such as Figure 1 would result. Of course, these effects have been demonstrated experimentally only and have not been confirmed in human beings.

EFFECT OF LOW SALT DIETS ON HYPERTENSION

Ambard and Beaujard⁴ were probably the first to recommend a salt-poor diet for the treatment of hypertension. Later Allen and Sherill²⁶ strongly advocated this meas-

ure as did Volhard.²⁷ Other investigators have obtained effects with this diet and various theories have been proposed to account for them, while many others were not convinced of its efficacy. Diets of this type came into rather wide use in Europe but were not generally applied in this country. Recently, however, a renaissance of this subject has occurred (Table 1), principally because of the work of Kempner.²⁸ By applying a diet of rice, fruit juices and vitamins to the treatment of hypertension, he found consistent and significant reductions in blood pressure in about 57 per cent of patients. This diet contains less than 200 mg. of sodium. Recently, Grollman et al.¹⁶ studied six patients on a diet containing less than 1 Gm. of sodium chloride. A significant fall in blood pressure occurred in two, with slight reduction in three others.

Probably the most complete work on the subject was done by Viersma.²⁹ His experiments appear to be the most extensively controlled and deserve attention. He studied eight patients suffering from so-called "essential" hypertension, two from chronic nephritis and four from malignant hypertension. Observations on one patient ex-

tended for more than two and one-half years. His control periods were long and carefully standardized. In seven of the ten patients with "essential" hypertension or that secondary to chronic nephritis, blood pressure became lower under the

Viersma found no reasons in his own work and in an extensive review of the literature to assume the existence of any abnormalities of sodium chloride metabolism in "essential" hypertension. In the malignant stage, however, even when renal

TABLE I
SUMMARY OF RESULTS REPORTED IN THE RECENT LITERATURE

Author	Type of Diet or Sodium Content mg.	No. of Patients Treated	(O) Out-patients; (H) in Hospital	No. Affected Favorably	Change in Diastolic Pressure mm. Hg	Per Cent Afflicted	Remarks
Bryant and Blecha ³⁰	200	45	O	26	>30 >20-29	18 40	
Kempner ²⁸	Rice (200)	47 50 65	H H H	25 20 12	>20 >20 >20	53 40 18	Renal disease primary Renal disease secondary Renal disease absent
Grollman et al. ¹⁶	200	6	H	2	>20	33	
Filipse and Filipse ³⁵	200	32	O	13	>20	41	
Viersma ²⁹	400	8	H	2	>20	25	"Essential" hypertension
	400	4	H	1	>20	25	Malignant hypertension
	400	2	H	2	>20	100	Nephritis, chronic
Schroeder et al. ³²	Rice (200)	6	H	1	20	17	
Behrendt and Burgess ³⁶	Rice	9	H	7	Average pressures reported Diastolic change < 20 mm.

influence of a diet containing less than 1 Gm. sodium chloride per day. Viersma concluded, however, that the decline was not great, the systolic pressure falling 40 mm. Hg or less and the diastolic 26 mm. Hg at the most. Ingestion of this diet was associated with oliguria but had no demonstrable effect on renal function except in one subject. In this instance, low grade uremia became worse when treatment with ammonium chloride and salyrgan produced a sodium chloride deficiency. The diastolic pressure decreased further when this occurred. In cases of malignant hypertension the salt-poor diet had little effect on blood pressure. In general, but with exceptions, he found that changes of blood pressure during salt retention or loss paralleled changes in blood volume although variations were relatively small. He also noticed that changes in blood pressure lasted for a long period after return to a normal diet.

function was good, he found that salt was lost by the kidneys. He did not believe that the adrenal cortex was involved in the effects noted, but that they occurred because of a decreased cardiac output resulting either from a change in blood volume or from some reduction in peripheral and elastic resistances.

Among others who have recently studied the effects of this diet upon the blood pressure of hypertensive patients, Bryant and Blecha³⁰ found a significant lowering of diastolic pressure (20 mm. Hg or more) in 57.8 per cent of patients treated with diets containing less than 200 mg. of sodium. These were outpatients and blood pressures were all ambulatory readings. Dock³¹ states that about half of the patients in his series were benefited by low salt regimens.

Our own experiences, both with a diet containing 1 Gm. of sodium chloride and with Kempner's rice diet, have been disap-

pointing. Although the series was small, patients were carefully controlled in a hospital. One Gm. salt diets were found to be relatively ineffective in patients with severe arterial hypertension and were not used extensively.³³ After at least a month in the hospital on a normal diet containing salt, the institution of salt restriction was not observed to affect the blood pressure significantly when used for a period of two to eight weeks. On the other hand, decided depression of the blood pressure to normal or near normal was observed in occasional patients. For example, a forty-two year old woman with some of the signs of Cushing's syndrome showed considerable edema and a disturbance of water excretion characterized by a low urine volume which was relatively unaffected by varying the intake of fluids. Her urine contained antidiuretic substance. Coincident with the use of a diet containing 1 Gm. of sodium chloride her blood pressure fell to normal levels from approximately 220 mm. Hg systolic and 120 diastolic. Occasionally, other patients responded similarly. These were in most instances women exhibiting obesity who were often at about the age of the menopause.

Six patients were studied carefully, using the rice diet of Kempner.³² Control periods in hospital extended for about a month in most instances. The institution of the rice diet did not change the average diastolic pressure of three patients with severe hypertension at all. In two others the fall was slight and in a third the average diastolic pressure fell 20 mm. Hg. The plasma chlorides fell in all patients, but in two in whom plasma sodium levels were followed there was little change. This was also noted by Viersma²⁹ and no explanation is offered. The one patient in whom the diastolic change occurred exhibited obesity, easy bruising and a reduction in tolerance to glucose. She had at one period of her life taken insulin. The administration of sodium chloride to this diet was not accompanied by consistent changes in the opposite direction as far as blood pressure was concerned.

It was concluded that the rice diet had little advantage over a normal diet low in salt and that the change expected was minimal and occurred in those patients with less severe manifestations of their disease. While these studies were not as extensive as those of Viersma, the conclusions were similar, i.e., that the changes expected when the subjects are well controlled are slight. The diet is a rigorous ordeal for most patients and is hardly justified unless it can be shown to have special advantages.

It should be pointed out that adequate control periods are essential in judging the effect of any procedure upon the blood pressure in hypertension. It is an axiom that any therapeutic procedure vigorously pursued and instituted for the relief of "essential" hypertension will lower blood pressure and a corollary that nothing so far discovered is specific for the disease. We believe that the control period must be carefully evaluated and that the blood pressure must be at the lowest stable level for a considerable period of time before any procedure is instituted. Viersma studied some patients as long as three and one-half months without doing anything. The very fact of treating the patient, as well as rest and hospital routine, will often produce decided effects.

In Kempner's studies, when he found declines in blood pressure in twenty-eight of fifty patients with renal disease and in thirty-seven of sixty-five without renal involvement, control periods which we consider adequate were not indicated. In his published charts they varied from seventeen to four days, the average being nine days.²⁸ In Grollman's series the control periods were somewhat longer, but in no patient were these periods more than two weeks.¹⁶ Controls in other recent studies have not been published, yet it is only by long periods of control, impossible in most general hospitals, that one can evaluate adequately therapeutic procedures of this kind. One recent study was well controlled, but the effects on the diastolic pressure did not appear to be marked.³⁶

A small group of female patients has been studied who appeared to respond favorably and sometimes dramatically to a reduction of sodium chloride intake.³³ We have a clinical impression that many of these patients exhibit certain common findings which occur to a more marked degree in Cushing's syndrome. For lack of a better term, they have been called "pseudo-Cushing's."^{*} They are usually obese with the obesity often confined to the trunk. They bruise easily and exhibit a curious mottled cyanosis of the skin especially of the extremities. They sometimes show an abnormal tolerance to glucose of a type resembling diabetes. Rarely has osteoporosis been found. There may be associated menstrual disturbances or the menopausal state. Hirsutism has occasionally been noted. The possibility exists that these subjects represent a separate disease which hypertension is associated with secondarily. If the activity of the adrenal cortex is found to be altered in these patients, their hypertension might be on that basis. On purely clinical grounds that suggestion is possible. The response of their blood pressure levels to salt restriction may indicate that salt is concerned in their hypertension.

If salt-poor diets do lower blood pressure in some cases, when psychotherapeutic influences are excluded, this must be explained. Adequate explanations are lacking. It is difficult to understand how retention of salt *per se* can raise blood pressure unless circulating blood volume is increased. The theories proposed are in the main unconvincing in the light of other and more direct evidence for different mechanisms. Grollman³⁴ believes that there may be some reduction in extracellular fluid resulting in a diminished plethora of the vascular system. Still, explanations of the mechanism of the lowering of blood pressure by the use of a low salt diet remains as unclear as does the inconsistency of response in different patients.

One of our patients who was put on the

^{*} Term suggested by Dr. Willard M. Allen.

diet had exhibited diminution of renal function without nitrogen retention. After two weeks on the rice diet she became drowsy, disoriented and developed nitrogen retention and diminished urine volume. When her plasma chloride and sodium content were finally measured, they were at levels of 118.4 and 69.0 mEq./L., respectively. She died in uremia without significant change in the level of her blood pressure. This case is mentioned for two reasons. First of all, it can not be too strongly stressed that a low salt or rice diet can bring on fatal consequences when renal function is reduced. We have observed the same sequence of events in patients suffering from congestive heart failure after severe salt depletion from the use of mercurial diuretics. Secondly, the fact that this patient's sodium and chloride levels in plasma and presumably in her whole body were reduced markedly without change in blood pressure, suggests that sodium chloride was not concerned in the mechanism of the elevation of her blood pressure. Viersma believes that blood volume changes may account for the results observed but it is difficult to conceive of this mechanism as the principal factor. The explanation is unclear and the mechanism unknown.

It is our present belief, however, that certain patients will respond to a low salt diet with reduction in blood pressure. Some of these patients may be suffering from a disease different from that commonly considered to be "essential" hypertension. Slight changes may be observed in other patients. These are probably due to secondary influences and not primarily concerned in the mechanism of the elevation of blood pressure. On the whole, in our experience those patients with the most severe degree of hypertension respond to salt restriction least. And this is the group which it is necessary to help.

Until more is known about the subject it is therefore advisable to try diets low in salt for the routine treatment of hypertension with the expectation that a majority of patients will not respond. When renal

function is reduced, this should be done under conditions in which the patient can be carefully watched and plasma chloride levels followed. If the response is good, the diet can be continued; if not, stopped. The rigors of the so-called rice diet are hardly justified considering that similar results can probably be obtained by rigid restriction of sodium chloride alone.

The diets used should contain as little salt as possible, depending upon the response of the patient. One Gm. of sodium chloride may be too much in some individuals. Approximately 0.5 Gm. is about as low as can be maintained under the best conditions. Both of these diets require careful selection of foods and fluids and are usually difficult to maintain when patients are ambulatory. It is hoped that methods other than dietary ones for controlling blood pressure will make this difficult and unpredictable form of therapy obsolete for the majority of patients exhibiting so-called "essential" hypertension.

SUMMARY

The dietary management of arterial hypertension by the use of diets poor in sodium chloride is discussed. The possible rôle of the adrenal cortex in arterial hypertension and its relation to disturbances in salt balance is considered in the light of experimental and clinical evidence. While many subjects do respond favorably to rigid restriction of salt by lowering of blood pressure, psychotherapeutic influences may play a large part in this change in some. If subjects are adequately controlled, the change to be expected is not great and may be absent in patients with severe hypertension in whom therapy is most needed. It is possible that patients who do respond favorably to this diet exhibit a different type of hypertension in which the adrenal cortex is overactive. The mechanism of the response is not understood. No special advantage has been demonstrated in the use of a diet exclusively composed of rice, fruit juices and vitamins, as compared with a

normal diet with a similar content of salt, and there are several disadvantages to it.

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Impulsive Behavior in a Crippled Boy*

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital, in which the Orthopedic Service cooperated.

DR. HENRY H. W. MILES: J. T. (No. 462356), a seventeen and one-half year old boy, was referred to the Psychiatric Service from Orthopedics because of his despair over his left thigh, resentment toward the world in general and violent outbursts of physical aggression. He had had osteomyelitis of the left femur for nearly three years, with various complications, culminating in a pathologic fracture. Following this, he had worn a succession of spicas for nine months, then had the misfortune of re-fracturing the femur just when his progress appeared to be encouraging. It was at this point that he was first seen by a psychiatrist.

The patient's past medical history was noteworthy. At about four and one-half years of age he was hit by a car and bumped his head. The extent of this injury was not known, but the patient believed he was kept in bed by the doctor for two weeks. His left femur was fractured when he was five. At six he had a tonsillectomy. He developed septicemia at the age of nine and was hospitalized for a year. At eleven his left elbow was fractured. When the patient was fifteen, an abscess developed on the left thigh which was incised and drained. This was followed by osteomyelitis for which there have been eight hospital admissions and a number of operations. On four occasions he had had ether anesthesia, each time with severe anxiety.

The boy's parents were both high school graduates of English extraction. The patient had been told that they were never really married and this worried him. His birth and early development were said to have

been normal and there were no childhood neurotic traits except temper tantrums. When he was eighteen months old, his parents separated, ostensibly because of the father's alcoholism and infidelity. The patient was sent to his grandmother, then back to his father who had remarried. His stepmother had two children of her own and rejected the patient so he was finally placed in an orphanage when he was six. There he remained for five years, learning that fighting and stealing were the best ways to achieve prestige. When he was eleven, he went back to his mother, who also had remarried and had a two year old son by the second husband. The patient liked his stepfather, a rather friendly, outgoing man, but soon showed jealousy of his half brother. Outbursts of aggression appeared, once to the point of attempting to choke the little boy.

The patient said that at school he deliberately provoked the teachers and gained a reputation of being a "tough guy." He hoped to be expelled and probably would have been except for the intervention of osteomyelitis. This started when he was in the eighth grade and he never went back to school. About sexual matters he had always been shy. At the age of eleven he developed poison ivy on his genitals and endured severe itching and swelling rather than tell his mother or a doctor. A few years later he was quite upset when his mother had an extramarital affair, and it was about this time that he had fears of a man coming into his room at night to kill him. There were occasional nightmares of being shot

* From the Psychiatric Service of the Massachusetts General Hospital, Boston, Mass.

or stabbed by a man. He masturbated occasionally with feelings of guilt but was unable to tell about this in detail.

Since the time he left the orphanage, the patient had tried to be older and tougher than he really was. He took exercises to build himself up, began to swear, smoke cigars and drink. He loved to get into fights and make other boys cry. Since the beginning of the osteomyelitis, he had become more aggressive and he related numerous fantasies of smashing people in the face, shooting, killing and robbing.

Physical examination was normal except for large scars on the left thigh and disuse atrophy. Complete blood count and urinalysis were normal and x-ray of the chest was negative. Basal metabolic rate was -11. X-ray of the left femur showed marked osteoporosis of areas adjoining the fracture, with incomplete bridging of the fracture by new bone formation and a possibility of sequestration. The electroencephalogram was a borderline record.

The patient's general behavior and manner of speech had a veneer of belligerence, beneath which the mood was one of anxiety rather than aggression. Memory and orientation were normal, general information fair, judgment and insight poor.

After the initial study, therapeutic interviews were begun. A number of hours were spent on his hostility and ventilation was encouraged. It seemed that the patient's anger developed frequently in situations in which he believed others thought him inadequate or weak. He poured out a tremendous number of violent fantasies in which he was vengeful or aggressive. His anxieties, however, were always near the surface, and he told how terrified he was of ether because it might kill him or the doctors might trick him and amputate his leg. He talked about his mother and how much he hated her because she did not love him; but he had a strong attachment to her and related how he was so angry with her lover that he threatened to kill him with a knife. The patient would talk repeatedly about a girl who had shown

interest in him and how he was attracted to her and at the same time uneasy. Finally he stated that being near girls made him shaky and sweaty so he had to keep them away by his roughness of manner. This led him back to his fears of ether and he related a dream, associated with his first operation, in which he dreamed he was dead. He then told a story of a Japanese war atrocity in which wounded 'prisoners' testicles were smashed with a hammer. He talked spontaneously and no interpretation was made to him.

When the hip spica was removed for an orthopedic check-up, the patient became tense, restless, profane and at the same time felt very tired, had "empty" feelings in his chest and felt limp. He disrupted ward morale by smashing windows and threatening suicide. He was afraid to go to sleep at night because something might happen to his leg. We then discussed his feelings about girls and he became reticent. His anxiety was demonstrated, however, by another violent outburst during which his behavior was even more impulsive. It was decided that he could no longer be kept on the ward and when he was told he became upset, anxious and threatened to kill himself as soon as he got out. He then said there was something he wanted to tell but was unable to say it. Finally he wrote it out, describing how he thought his mother had purposely made herself sexually attractive to him and how this had made him masturbate. He related fantasies of raping her and of killing his stepfather so he could possess his mother.

SOCIAL SERVICE REPORT

MISS BEATRICE TALBOT: The patient's mother was a rather immature woman who never took any initiative about her son's plans. She wrote him simple, chatty letters. His stepfather was a happy-go-lucky, wise-cracking sort of man. The patient had not seen his own father for ten years. The patient's paternal grandmother was an energetic woman and a strong Christian Scientist. He was appreciative of what she

had tried to do for him, but usually became fresh and insulting in her presence and was bothered by her attempts to force her religion on him.

The patient was so upset whenever he went home that one of my main functions was to try and arrange to have him stay in Boston. He had lived with his paternal grandmother at a nursing home which he hated, and at a boys' nursing home which he had to leave because they could not look after him medically. There was no member of his family who could give him a home.

The patient had several talents: drawing, writing and singing. He had considerable persistence but had difficulty accepting criticism. The State Department of Rehabilitation would arrange for a training program if he were well enough to pursue it. The Goodwill Inn offers a living place for boys with social guidance and an opportunity to work. They would accept this patient.

PSYCHOLOGIC REPORT

DR. FREDERICK WYATT: The Rorschach test showed an intelligence quotient between 110 and 120, probably higher because neurotic difficulties interfered with his performance. His responses indicated: (1) Breadth and sensitivity of approach; (2) inhibition of the free use of imaginative faculties due to disturbance of self-regard and constriction of mental activities because of frightening preoccupations; (3) use of his mind in a repetitious pattern of conflict; (4) tension states which resulted in violent discharges; (5) he was friendly although antagonistic at times, and he had a frustrated need for love; (6) there was more need for dependency than the patient could accept; (7) he was worried about his body.

Diagnostic Impression: Psychoneurosis, violent outbursts, character disturbance.

PATIENT INTERVIEW

The patient entered the conference room for brief examination and interview. He was a slim, medium-sized boy on crutches.

Nothing new was brought out on physical examination. The interview before the group showed a lad with apparent cooperation and ability to speak up in front of a group, but he looked anxious, talked tough, had a hostile intonation and mien although his answers were civil enough. He explained that when he "gets nervous" he impulsively does things he is sorry for and that he does not know why he acts that way. His anxiety over having his leg examined and x-rayed was connected with his fear that the leg would be no good or would have to be amputated. "How could I do a man's work without a leg"?

DISCUSSION

DR. MARY A. B. BRAZIER: The electroencephalogram was abnormal, with localization in the right occiput. This kind of variation is found in less than 10 per cent of normal people.

DR. STANLEY COBB: Under diagnosis we must consider psychopathic personality and neurosis. About one-half the psychopaths have abnormal electroencephalograms; many of these have a history of head injury. This boy's behavior was that of a psychopathic personality. These people may be classified under three headings: (1) Hereditary psychopathy; (2) those with abnormal electroencephalograms related to head injury and encephalopathy; (3) character neuroses. The inherited ones are "bad eggs," literally speaking, and the prognosis is not good. The second class is allied to epilepsy and is treated with dilantin or benzedrine without much optimism. Treatment of character neurosis is more hopeful. Which was this boy? How should we handle him? It looked as if the administration would be unable to permit us to keep him here.

DR. LEMOYNE WHITE: Last night he escaped from the ward and stood in the hall cursing loudly, saying he was going to break the doors down. He went back to his room at my request, apologized and said he did not know why he got that way. He said he would promise to be good if he could go

back to the open ward. I did not grant his request and he returned to his room laughing hysterically and said: "I don't care, I like it here. I like it here." He asked for liquor, said he would break out and shoot everybody and that he now had the guts to commit suicide. He hurled himself against the window with enough force to break an ordinary screen. It was an impulsive act with all the power he had. He fell to the floor in a heap and burst into tears. He repeated this cycle at intervals until 12:45 A.M. when I told him firmly that if he continued such behavior he would have to leave.

DR. BERNARD BANDLER: The abnormal brain waves and impulsive behavior suggest postencephalitic behavior. His heredity was bad; one could label both parents as psychopaths. He was suspicious of everyone. The clinical picture was disturbing. There was a real danger that he might kill himself or someone else if handled badly. He had not shown this extreme behavior in the past and I wonder what had mobilized it. He had been encouraged to express his aggressive feelings and he was already terrified of losing control of them. Perhaps pushing him to talk about these feelings and about sex had mobilized his anxiety. The purpose of bringing him here was to allow him to have a relationship which would be safe. He got angry when he felt weak; for example, when people gave him a seat on the subway. He wanted to be a "big shot"; he smoked cigars and drank as a defense against being crippled. He could do something constructive in occupational therapy and have exercise that would develop power in his hands and shoulders. The most important current situation was the orthopedic one and I would let him express his anxiety about it.

DR. COBB: If you want a dynamic explanation, we could say we never saw anyone who was more rejected. He actually believed his mother and father wanted him put out of the way, wanted him killed. In reverse he said he would like to kill them. That is enough to give a normal person a

severe neurosis with great inferiority feelings. In addition he had fears about his manhood and about his erotic attachment to his mother. It was a complex neurotic situation plus whatever encephalopathy existed.

DR. HERBERT BARRY: Dr. Bradley helped problem children with amphetamine sulfate. This patient was a little old, but it might be worth trying to see if it would make him comfortable enough to work with him. Also I believe it would be wise to separate disciplinary authority from the doctor who does the interviewing. I would now try to make interpretations on the basis that if you want to get material, you probe and bring up anxiety; if you want to relieve anxiety, you make interpretations.

DR. COBB: His fear of losing his leg was very important. It meant to him that he could not be a man.

DR. ELSE NEUSTADT: This patient had a good intellectual endowment which had never been developed. Could something be done with that?

MISS THEODORA KALEM: He had done some fiction writing and he had some talent for drawing.

DR. EDUARD HITSCHMANN: He found no love in his family, always hate. He was castrated in many ways. If he found an occupation, a job, his character would improve.

DR. COBB: One might consider a pneumoencephalogram to see if he had any cerebral atrophy. I would be against it because the boy would resent the procedure and because the findings would not affect our therapy. The head injury was thirteen years ago. The abnormal electroencephalogram might be due to heredity or to an old head injury; there is one chance in ten that such an electroencephalogram could occur in a normal person. We are therefore probably dealing with a boy who has poor heredity and perhaps an injured brain. We could call him a psychopath and make no effort to treat him. But there is a large anxiety element. From the therapeutic standpoint he has assets. He is likeable, likes to work

and has ability. In psychoanalytic terms, his neurosis is due to rejection, castration and to an Oedipus situation. He has produced evidence that he is not wanted at home, that he fears he will lose his manhood and that he has an erotic attachment to his mother. These problems must be talked out with him further. Also his anxiety must be eased by explaining his behavior to him and by giving him some satisfactory occupation. This can be done by discharging him to a living situation in which he will have satisfying work and by having Dr. Miles continue to see him in psychiatric interviews. The prognosis is uncertain because of the precarious social situation, but with the boy's good assets therapy is well worth trying. Beside the work and interviews he should have a trial of dextro-amphetamine sulfate, 10 mg., at breakfast and noon.

FOLLOW-UP NOTE

During the eight months since discharge from the hospital the patient has been seen about twenty times for psychotherapeutic interviews. He left the hospital with his father who had somewhat reluctantly agreed to assume responsibility for the boy rather than see him committed to a state hospital. This was the first time the patient had seen his father since early childhood and he was at first pleased with the arrangement. It soon became evident, however, that the patient's explosive outbursts and irritability were causing serious friction with the stepmother and her six children. Several interviews were concerned with current material and the patient was allowed to ventilate his feelings. He spontaneously brought up sexual topics, but on the one occasion on which deeper probing was attempted he suddenly developed severe headache and dizziness. This was interpreted to him as his reaction to the anxiety-producing topic and reassurance was given.

The situation at home grew worse and he came to Boston to live with his grandmother. More interviews were possible and the orthopedist discussed open reduction.

The patient was made anxious and sleepless by this. Also his stepmother wrote that he could not return to them because she was pregnant. During the next month interviews were frequent and a great deal of reassurance was given. Anxiety over sexual thoughts and fantasies was prominent, and from the material it was possible to point out to him how his aggressive outbursts were frequently related to his feelings of sexual inadequacy. He was encouraged to talk about the operation. In spite of the hateful ideas expressed in interviews his behavior was good. After repeated orthopedic examinations it was decided not to operate and the patient was told to walk with a cane. His mood improved dramatically, and he found a job as an apprentice dic cutter.

The patient's first job lasted only two weeks when, through an unavoidable circumstance, he was transferred to a jeweler's shop as an apprentice. After a night of drinking he impulsively stole a wrist watch and pawned it to get more liquor. He was arrested promptly and was frightened to discover that the watch was worth \$500.

After the case was investigated the patient was released on a year's probation. He was very discouraged, thought that "the cops would be watching him all the time" and again began drinking and making threats of violence.

When last seen, about four weeks later, he seemed better. He had rented a small apartment for himself, a friend and his grandmother and was planning to paint and decorate it. The prospect of another job was encouraging and the destructive and violent fantasies were less.

CONCLUSION

This case of severe personality disturbance in a crippled, adolescent boy might be diagnosed variously by different psychiatrists. The diagnosis of psychopathic personality carries with it an implication of therapeutic hopelessness, and therefore it was thought preferable to regard the

illness as a neurosis. The interview material allowed a dynamic explanation of the symptoms in terms of early parental rejection which aroused tremendous hostility and insecurity, typical mutilation anxiety and unresolved erotic attachment to his mother. On this basis the outlook was considered more hopeful.

A probing type of psychotherapy mobilized anxiety and the patient began "acting out" his neurotic conflicts in an impulsive manner. It was then decided that further treatment should be of a supportive nature. The therapist allowed the patient to ven-

tilate current problems, but avoided anxiety-laden topics, and reassured him freely. The patient was encouraged to stick at his job as a further means of bolstering his self-esteem. These measures were intended to reinforce, if possible, the patient's repressive mechanisms. Interest was shown in his painting and short stories, through which he expressed many aggressive fantasies.

It was believed that marked improvement could scarcely be hoped for; but if this boy could be prevented from becoming an alcoholic or a criminal, the efforts at therapy will have been well spent.

Clinico-pathologic Conference

Hemoglobinuria and Cardiovascular-Renal Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. C., (B. H. History No. 139562), a fifty-six year old white, married carpenter, entered the Barnes Hospital for the first time on September 19, 1946, complaining of weakness and jaundice. The family history was irrelevant. In regard to the past history the patient had been told that when he was two years old he had had rheumatism but he stated that he had enjoyed excellent health until two years before admission; at that time he had an episode of "pleurisy" from which he recovered without event. Systemic review was non-contributory. The patient had spent most of his adult life working as a farmer or a carpenter and his habits were good.

About twenty-one months prior to entry he developed sudden pain in the calf of his left leg. The pain was so severe that he was forced to walk with the aid of crutches for several days. He denied any parasthesias or weakness and had not noted either redness or swelling of the extremity but the pain was made worse by motion. The pain spread to involve the muscles of the thigh and the patient became almost totally incapacitated. He was seen by a physician who made a diagnosis of pernicious anemia and gave him injections of liver twice weekly. The patient stated that at the time of this illness his urine had a reddish-brown color. After about six weeks the pain in the leg disappeared and the patient was again able to work until one year before entry

when he noted the onset of progressive weakness associated with attacks of dizziness which followed exertion. The symptoms were relieved by rest. This group of symptoms persisted and seven months before his admission he developed difficulty in taking fluids; he noted that they would spill out of the right corner of his mouth. No other neurologic manifestations occurred but his physician told him at the time that he had had a "slight stroke." At the same time the physician noted a yellow color to the patient's skin which had persisted from then on. His urine became still darker; its color, which was described as "wine or dark brown," was attributed by the patient to the taking of a new medication called "Ventrax."

Two or three months prior to entry the patient passed tarry stools for a short period but had no other digestive symptoms. His weakness continued to increase so that even a short walk served to tire him excessively. One month before admission the patient had an episode of sudden complete deafness which lasted only one and one-half hours. Gradually hearing returned and was maintained. Following this episode he sought admission to the Barnes Hospital. In the ten months prior to hospitalization he had lost 30 pounds.

Physical examination at the time of entry revealed the patient's temperature to be 37.6°C., pulse 92, respirations 18 and blood pressure 190/100. He was a well developed,

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

well nourished male in no acute distress but he appeared chronically ill. Jaundice of the skin and sclerae was easily seen. The pupils reacted well to light and accommodation. Examination of the fundi revealed tortuosity of the arterioles but no hemorrhages or exudates. The ears appeared normal to examination. The tongue was not atrophied nor was it abnormally red in color. The teeth were in poor condition. The tonsils were large and cryptic. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was enlarged 12 cm. to the left of the mid-sternal line in the fifth interspace; the rhythm was regular. At the apex a soft blowing grade II systolic murmur was audible and at the left border of the sternum in the fourth interspace a grade II, high-pitched, early blowing diastolic murmur was heard. Examination of the abdomen revealed that the liver edge was palpable 4 cm. below the right costal margin and was sharp and firm to touch. The tip of the spleen was hard and descended 1 to 2 cm. below the left costal margin. On rectal examination the prostate was not enlarged and no other masses were felt. The neurologic examination was within normal limits.

The laboratory data were as follows: Blood count: red cells, 1,930,000; hemoglobin, 6.5 Gm.; white cells, 6,750; differential count: juvenile forms, 1 per cent; stab forms, 13 per cent; segmented forms, 68 per cent; lymphocytes, 16 per cent; monocytes, 2 per cent; reticulocytes, 11 per cent. Fragility test: normal. Urinalysis: albumin, 4+; Bence-Jones protein, negative; benzidine test, 4+; hemosiderin, present; sediment, many granular casts; no red cells. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 25 mg. per cent; total protein, 7.3 Gm. per cent; albumin, 4.5 Gm. per cent; globulin, 2.8 Gm. per cent; alkaline phosphatase, 1 Bodansky unit. Icterus index: 80. Cephalin-cholesterol flocculation test: negative. Bromsulfalein dye retention: no dye retained in thirty minutes. van den

Bergh test: direct, 9.7 mg. per cent (fifteen-minute reading); indirect, 2.1 mg. per cent. Venous pressure: 110 mm. NaCl. Circulation time (decholin): 14 seconds. Electrocardiogram: depression of S-T 1 and 2; T waves: low upright in lead I, diphasic in lead II, inverted in lead CF₄; slight slurring of all complexes. Special hematologic studies: sternal bone marrow, hypercellular with 588 normoblasts and 83 erythroblasts per 100 white blood cells. Acid hemolysis test: control cells plus patient's serum, no hemolysis; control cells plus patient's acidified serum, no hemolysis; control cells plus control acidified serum, no hemolysis; patient's cells plus control serum, no hemolysis; patient's cells plus control acidified serum, hemolysis. Serum methemalbumin: present. X-ray studies: Roentgenogram of the chest: "There are adhesions from old pleurisy at the left costophrenic angle. The heart is within normal limits as is the aorta." Open films of the abdomen: "The spleen is slightly larger than normal. The left kidney shadow appears normal but the right seems small." Intravenous pyelograms: "The right kidney is atrophic and non-functional." Films of the skull: "The changes of hyperostosis frontalis interna are present." Films of the right shoulder and of the left knee: "The only abnormalities are those of hypertrophic osteo-arthritis."

During his hospital stay the patient was put on an hepatic regimen. He received four blood transfusions and his red blood count rose to 2,500,000. He continued to pass dark urine and it was noted that the urine passed during the night was much darker than that passed during the day; the urine consistently contained hemoglobin. The patient remained jaundiced for about three weeks; subsequent examination of the serum revealed no abnormal pigment. Radioactive iron was administered in order to study absorption and excretion of that element, but soon after its administration the patient insisted on leaving the hospital because he felt well. During his stay his temperature had been slightly elevated, averaging about

37.8°C. He left the hospital on October 4, 1946.

He did well for several weeks but ten days before his second admission he again began to note shortness of breath on moderate exertion and experienced episodes of paroxysmal nocturnal dyspnea; he required two pillows under his head at night. Concomitantly, his urine became dark, weakness increased and anorexia developed. He was re-admitted to the Barnes Hospital on November 19, 1946.

At the time of entry physical examination revealed the temperature to be 38°C., pulse 120, respirations 24 and the blood pressure 210/120. The changes from those recorded on the first admission were as follows: The patient was quite dyspneic and orthopneic. Jaundice was less intense than it had originally been on the first admission. Increased tactile fremitus and dullness to percussion were noted at the bases of both lungs. On auscultation of the heart occasional ventricular premature contractions were heard and a protodiastolic gallop rhythm was audible at the left sternal border in the fifth interspace. The liver edge was felt 8 cm. below the right costal margin and was slightly tender. The spleen extended 3 cm. below the left costal margin.

Laboratory findings on this admission were as follows: Blood count: red cells, 1,920,000; hemoglobin, 8 Gm.; white cells, 6,750; differential count: stab forms, 5 per cent; segmented forms, 74 per cent; lymphocytes, 17 per cent; monocytes, 4 per cent. Platelets, 330,000. Reticulocytes, 20 per cent. Blood indices: mean corpuscular volume, 112 cubic micra; mean corpuscular hemoglobin, 38 gamma gamma; mean corpuscular hemoglobin concentration, 35 per cent. Blood chemistry: nonprotein nitrogen, 38 mg. per cent; total protein, 5.4 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.1 Gm. per cent. Icterus index: 120. Cephalin-cholesterol flocculation test: negative. van den Bergh test: direct, 0.8 mg. per cent; indirect, 2.10 mg. per cent. Blood culture: negative. Venous pressure: 195 mm. of saline. Circulation time (decholin):

26 seconds. Electrocardiogram: as before. Roentgenogram of the chest: "There is a moderate amount of fluid at both bases and marked cardiac enlargement."

Following discharge, the patient took 0.2 mg. of digitoxin daily, rested a good part of each day and felt quite comfortable. About three weeks before his third and final entry to the hospital he developed a cough productive of a small amount of white sputum. Concomitantly, slight swelling of the ankles and marked shortness of breath appeared and once again he had to sleep propped up in bed in order to breathe comfortably. These symptoms persisted and two weeks before entry the patient developed sudden severe pain in the left upper quadrant of the abdomen which did not radiate but which was aggravated by deep breathing. Two days later his urine appeared to be "black"; he stated that its color was definitely different from that previously observed and attributed the change to the taking of "black medicine" which his physician had given him. The black color disappeared from the urine when the patient discontinued the medicine. The abdominal pains, however, persisted and were severe enough to necessitate the use of codeine for relief and finally on January 14, 1947, the patient was re-admitted to the Barnes Hospital.

At the time of entry his temperature was 37.8°C., pulse 100, respirations 34 and blood pressure 180/90. Changes from the physical findings on his second admission were as follows: The patient was acutely ill and extremely dyspneic, so much so that he was unable to talk. He apparently suffered severe abdominal pain. The skin was grey in color. The sclerae were slightly icteric and the conjunctivae were markedly pale. Slight venous distention was noted in the neck. Examination of the lungs revealed them to be clear to percussion and auscultation. A blowing systolic murmur was heard at the apex of the heart and was also audible along the left sternal border but no diastolic murmur could be made out. The liver was the same size as noted on the earlier

examination but the spleen was not palpable. It was noted, however, that the patient held his abdomen quite rigidly because of pain and adequate palpation was therefore difficult. Two plus pitting edema of the lower extremities was present. Neurologic examination was within normal limits.

The laboratory studies were as follows: Blood count: red cells, 1,210,000; hemoglobin, 5 Gm.; white blood cells, 14,300; differential count: as before. The red cells were microcytic and there was 3 plus anisocytosis. The platelet count was 700,000. Urinalysis: color, brown; albumin; negative; sugar, negative; sediment, occasional granular cast; bile, negative; benzedine test, 3 plus. Stool: guaiac negative. Blood chemistry: non-protein nitrogen, 62 mg. per cent; total protein, 5.4 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.1 Gm. per cent. Electrocardiogram: as before.

On admission it seemed clear that in addition to the extreme anemia the patient's cardiac insufficiency had likewise progressed to an advanced degree. Immediately following entry he was given 2 units of red cell residue slowly through a venous pressure apparatus and was placed in an oxygen tent. Two-tenths mg. of digitoxin was also given. Because of the abdominal pain a surgical consultant saw the patient. Among the diagnostic suggestions were perforated viscus and penetrating peptic ulcer. Because of the patient's critical condition, no surgical intervention was considered. Following repeated transfusions of red cells residue the red count rose to 3,000,000 and the hemoglobin to 9 Gm. Two days after entry the cephalin cholesterol flocculation test was 3 plus and the icterus index 112. On the third hospital day the patient received another transfusion. Shortly thereafter his temperature rose to 40°C. A few moist râles were noted at both lung bases and there was some dullness at the right base. The patient did not cough however and the white cell count was only 6,300. He was fluoroscoped and patchy infiltration was noted in the right lower lobe. Penicillin therapy was instituted. Urinalysis revealed 3 plus albu-

minuria but the urine did not exhibit an abnormal color grossly. Abdominal pain and distention were not relieved by symptomatic measures.

One week after admission, the patient's dyspnea had improved sufficiently to allow him to lie flat in bed. The venous pressure had fallen to 120 mm. of saline and a satisfactory diuresis was recorded. Nonetheless, the patient's general condition continued to deteriorate. The non-protein nitrogen rose continually to a final value of 158 mg. per cent, the carbon dioxide combining power fell to 25.9 volumes per cent and the chlorides to 94 mEq. per liter. Respirations were rapid and deep. During the twenty-four-hour period prior to death blood drawn at six-hour intervals showed no gross hemolysis. The patient became irrational, then comatose and a uremic frost appeared on his face. He failed to arouse from his coma and died quietly on January 25, 1947. During the final admission his temperature ranged between 38 and 39°C. until the last few days of life when it gradually fell to normal.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is indeed complicated and presents a number of interesting features. Most interesting, perhaps, is the hematologic problem, and we are fortunate indeed that Dr. Maxwell M. Wintrobe, Professor of Medicine at the University of Utah School of Medicine, is visiting us and will join in our discussion.

The patient appeared to be in good health two years before admission. Following an episode of pain in his lower extremity, he apparently developed anemia, passed dark colored urine and developed jaundice. When he was admitted to this hospital, his urine contained no red cells but the benzedine test was strongly positive and we infer, therefore, that he had hemoglobinuria. I think that before we define the hemoglobinuria further we should inquire into the mechanism by which it develops and I shall ask Dr. Carl Moore to open the discussion.

DR. CARL V. MOORE: Hemoglobinuria is usually associated with intravascular hemolysis. It distinguishes hemolytic anemia due to intravascular hemolysis from the types which are produced by destruction of red blood cells in the spleen. That is, hemoglobinuria indicates that red cell destruction is occurring within the vessels and in all probability the spleen has little to do with the process. The causative factors of increased intravascular hemolysis are numerous. Drugs, syphilis, severe exercise and infections all may cause intravascular hemolysis and hemoglobinuria. Hemoglobinuria does not usually appear until the level of free hemoglobin in the plasma has risen to about 135 mg. per cent.

DR. ALEXANDER: When free hemoglobin appears in the serum and the renal threshold is reached, some of the pigment will pass into the urine. What is the rôle of the kidney in regard to the appearance of hemoglobinuria?

DR. C. V. MOORE: No one really knows, but one group of investigators measured the amount of hemoglobin excreted by the kidneys very carefully and found that when the serum level reaches 250 mg. per cent of hemoglobin or higher the rate of excretion of hemoglobin is about 3 per cent of the theoretical clearance. They suggested that about 3 per cent of the glomeruli permit hemoglobin to pass and that with very low levels of hemoglobin in the urine the tubules can resorb it all. As soon as the level goes above the figure of 100 to 150 mg. per cent the tubular absorption falls behind the filtration rate and free hemoglobin then appears in the urine.

DR. ALEXANDER: This patient died in uremia and we therefore would like to inquire whether the kidney is itself damaged by the process which you have described.

DR. C. V. MOORE: Again, there have been few studies on the particular type of hemoglobinuria with which we are dealing here, if this indeed be paroxysmal nocturnal hemoglobinuria. Urea clearances have been carefully studied in several patients and

have been found to be normal despite prolonged continued excretion of hemoglobin.

DR. ALEXANDER: In other words you do not believe that we are justified in attributing the uremia to the hemoglobinuria.

DR. C. V. MOORE: I think that the uremia was more likely due to nephrosclerosis than to hemoglobinuria.

DR. ALEXANDER: This patient had a positive indirect Van den Bergh test and was jaundiced. In the conversion of free hemoglobin to bile pigment is there any structural damage to the liver? You will recall that his liver was enlarged.

DR. C. V. MOORE: Whenever there is hemoglobinuria and resulting hemoglobinemia, there may be focal necrosis of the liver. This man certainly might have had that lesion despite the negative cephalin-cholesterol flocculation test.

DR. ALEXANDER: The cephalin-cholesterol test did become positive on the final admission. Let us now consider the various types of hemoglobinuria. Dr. Moore has suggested paroxysmal nocturnal hemoglobinuria. Would you comment on the mechanism by which this disease arises, Dr. Wintrobe.

DR. MAXWELL M. WINTROBE: It is thought that there is an abnormality of the red cells *per se*; there is probably another factor which is suggested by the results of the acid hemolysis test. If that test is an index of what happens *in vivo*, it would seem that changes in the pH of the blood are important in the development of hemolysis. However, the fact that normal cells in the presence of acidified serum from this patient did not hemolyse indicates that changes in pH are not alone responsible and points to an intrinsic defect in the cells themselves. We really know very little about the pathogenesis of paroxysmal nocturnal hemoglobinuria and although it is certainly a definite clinical syndrome we can say little about its mechanism. These cases are rather rare; I believe only about fifty have been described in the literature and opportunity for a careful study is therefore not very often obtained.

DR. ALEXANDER: From what you say I would gather that the more acid the serum becomes the more hemolysis there would appear.

DR. WINTROBE: That is correct.

DR. ALEXANDER: Dr. Futcher, would you comment on pH changes which may occur in the blood?

DR. PALMER H. FUTCHER: It is possible that during sleep there is depression of the regulatory centers concerned with the respiratory adjustment of blood pH. During sleep, therefore, carbon dioxide may accumulate in the body and the blood pH may fall slightly. Such acidosis might precipitate hemolysis of abnormal red cells but I do not recall whether or not such measurements have actually been made.

DR. ALEXANDER: Dr. Moore, do you know whether such changes have been observed?

DR. C. V. MOORE: Dr. Ham made such studies and found that the pH in the serum never fell much below 7.2 at night. He postulated that the changes in the tissues might be greater than those measured in the blood but this concept has never been proven.

DR. WINTROBE: I think another factor to be considered is concerned with possible changes in the spleen. There may be alterations in the sinusoids of the spleen which are not duplicated in other intravascular spaces and which may lead to massive red cell destruction. Such a postulate is suggested by those few instances in which splenectomy is followed by improvement; against such an interpretation is the fact that in most instances splenectomy has been without any benefit whatsoever.

DR. FUTCHER: This patient did not develop hemoglobinuria until the age of fifty-six whereas I believe that in most instances the syndrome appears much earlier. I wonder if he would ever have developed hemoglobinuria had it not been for the acidosis which arose secondary to renal insufficiency.

DR. WINTROBE: Certainly very few cases have been described beyond the age of fifty.

DR. C. V. MOORE: I think that one case has been described in a woman who was fifty-two. If our diagnosis is correct in this instance, I believe it is quite strange that at the time the patient developed his most severe acidosis he did not have hemoglobinuria.

DR. FUTCHER: I agree and can offer no explanation for this confusing point.

DR. WINTROBE: I must say that I have a little doubt as to whether this man truly had paroxysmal nocturnal hemoglobinuria although I cannot make much of a case against the diagnosis except for the patient's age and the fact that absence of leukopenia and thrombocytopenia are unusual. When I read the protocol, it occurred to me that perhaps, for some reason or another, auto-agglutinins were produced in this patient's blood which led to his initial symptoms, for example, the pain in his leg which might have been due to a thrombosis, and that the subsequent history actually was one of repeated thromboses in various parts of his body.

DR. ALEXANDER: Is pain in the leg common in paroxysmal hemoglobinuria?

DR. WINTROBE: One may get thrombosis and thus pain in any region of the body.

DR. W. BARRY WOOD, JR.: Dr. Wintrobe, were you considering the possibility that this man had a carcinoma of the pancreas associated with multiple venous thromboses?

DR. WINTROBE: No, I was not thinking of any such specific mechanism. Very occasionally in atypical pneumonia, cold-agglutinins may be produced to such a high titer that hemolytic anemia occurs. However, here we have no story of pulmonary infection of that magnitude.

DR. ALEXANDER: Is there any specific lesion which at autopsy will enable the pathologists to diagnose paroxysmal nocturnal hemoglobinuria?

DR. WINTROBE: There is no specific lesion although hemosiderosis of the kidneys is perhaps the most consistent finding.

DR. C. V. MOORE: Dr. Wintrobe, in regard to your point concerning the absence of leukopenia, all of the white blood cell

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DR. C. V. MOORE: Whenever there is hemoglobinuria and resulting hemoglobinemia, there may be focal necrosis of the liver. This man certainly might have had that lesion despite the negative cephalin-cholesterol flocculation test.

DR. ALEXANDER: The cephalin-cholesterol test did become positive on the final admission. Let us now consider the various types of hemoglobinuria. Dr. Moore has suggested paroxysmal nocturnal hemoglobinuria. Would you comment on the mechanism by which this disease arises, Dr. Wintrobe.

DR. MAXWELL M. WINTROBE: It is thought that there is an abnormality of the red cells *per se*; there is probably another factor which is suggested by the results of the acid hemolysis test. If that test is an index of what happens *in vivo*, it would seem that changes in the pH of the blood are important in the development of hemolysis. However, the fact that normal cells in the presence of acidified serum from this patient did not hemolyse indicates that changes in pH are not alone responsible and points to an intrinsic defect in the cells themselves. We really know very little about the pathogenesis of paroxysmal nocturnal hemoglobinuria and although it is certainly a definite clinical syndrome we can say little about its mechanism. These cases are rather rare; I believe only about fifty have been described in the literature and opportunity for a careful study is therefore not very often obtained.

DR. ALEXANDER: From what you say I would gather that the more acid the serum becomes the more hemolysis there would appear.

DR. WINTROBE: That is correct.

DR. ALEXANDER: Dr. Futcher, would you comment on pH changes which may occur in the blood?

DR. PALMER H. FUTCHER: It is possible that during sleep there is depression of the regulatory centers concerned with the respiratory adjustment of blood pH. During sleep, therefore, carbon dioxide may accumulate in the body and the blood pH may fall slightly. Such acidosis might precipitate hemolysis of abnormal red cells but I do not recall whether or not such measurements have actually been made.

DR. ALEXANDER: Dr. Moore, do you know whether such changes have been observed?

DR. C. V. MOORE: Dr. Ham made such studies and found that the pH in the serum never fell much below 7.2 at night. He postulated that the changes in the tissues might be greater than those measured in the blood but this concept has never been proven.

DR. WINTROBE: I think another factor to be considered is concerned with possible changes in the spleen. There may be alterations in the sinusoids of the spleen which are not duplicated in other intravascular spaces and which may lead to massive red cell destruction. Such a postulate is suggested by those few instances in which splenectomy is followed by improvement; against such an interpretation is the fact that in most instances splenectomy has been without any benefit whatsoever.

DR. FUTCHER: This patient did not develop hemoglobinuria until the age of fifty-six whereas I believe that in most instances the syndrome appears much earlier. I wonder if he would ever have developed hemoglobinuria had it not been for the acidosis which arose secondary to renal insufficiency.

DR. WINTROBE: Certainly very few cases have been described beyond the age of fifty.

DR. C. V. MOORE: I think that one case has been described in a woman who was fifty-two. If our diagnosis is correct in this instance, I believe it is quite strange that at the time the patient developed his most severe acidosis he did not have hemoglobinuria.

DR. FUTCHER: I agree and can offer no explanation for this confusing point.

DR. WINTROBE: I must say that I have a little doubt as to whether this man truly had paroxysmal nocturnal hemoglobinuria although I cannot make much of a case against the diagnosis except for the patient's age and the fact that absence of leukopenia and thrombocytopenia are unusual. When I read the protocol, it occurred to me that perhaps, for some reason or another, auto-agglutinins were produced in this patient's blood which led to his initial symptoms, for example, the pain in his leg which might have been due to a thrombosis, and that the subsequent history actually was one of repeated thromboses in various parts of his body.

DR. ALEXANDER: Is pain in the leg common in paroxysmal hemoglobinuria?

DR. WINTROBE: One may get thrombosis and thus pain in any region of the body.

DR. W. BARRY WOOD, JR.: Dr. Wintrobe, were you considering the possibility that this man had a carcinoma of the pancreas associated with multiple venous thromboses?

DR. WINTROBE: No, I was not thinking of any such specific mechanism. Very occasionally in atypical pneumonia, cold-agglutinins may be produced to such a high titer that hemolytic anemia occurs. However, here we have no story of pulmonary infection of that magnitude.

DR. ALEXANDER: Is there any specific lesion which at autopsy will enable the pathologists to diagnose paroxysmal nocturnal hemoglobinuria?

DR. WINTROBE: There is no specific lesion although hemosiderosis of the kidneys is perhaps the most consistent finding.

DR. C. V. MOORE: Dr. Wintrobe, in regard to your point concerning the absence of leukopenia, all of the white blood cell

counts done were of course not reported in the protocol. On January 17th the patient's white count was 1,600 and the platelet count 133,000. Six days later the white count had fallen to 700

DR. ALEXANDER: Is leukopenia apt to be constant?

DR. WINTROBE: It is usually fairly consistent although occasionally with an acute exacerbation the count may rise.

DR. ALEXANDER: When this patient was first admitted to the Barnes Hospital, a chest x-ray revealed that the heart size was normal and the venous pressure and circulation time likewise were within normal limits. At that same time the electrocardiogram revealed a number of abnormalities and a diastolic murmur was heard along the left sternal border with a systolic murmur at the apex. No signs of cardiac decompensation had appeared. Two months later his heart had increased in size. The venous pressure and circulation time were greater and he complained of paroxysmal nocturnal dyspnea; that is, he developed all the signs of cardiac insufficiency. Dr. Massie, do you have any comment as to why cardiac insufficiency appeared?

DR. EDWARD MASSIE: This patient probably had hypertensive cardiovascular disease and, with the added load of a marked anemia, developed cardiac failure. He did have a history of rheumatism at the age of two years and if one were to consider the findings he might be able to make a fair case for rheumatic heart disease. There were systolic and diastolic murmurs; the latter certainly suggests aortic insufficiency. However, I think it is more likely that the diastolic murmur represented a hemic phenomenon and the hypertension certainly could have given rise to the systolic murmur. In subsequent examinations the diastolic murmur could not be heard and since aortic insufficiency due to rheumatic valvulitis should have at least persisted and probably would have progressed, I believe the evidence favors the interpretation that the aortic diastolic murmur was due to the anemia.

DR. ALEXANDER: Would you expect to find coronary damage?

DR. MASSIE: Very likely. Part of the enlargement may have been due to dilatation which accompanied the increased cardiac insufficiency as well as the effect of persistent severe anemia. It is well to point out, however, that if the patient had some degree of coronary sclerosis the additional burden of a severe anemia might have produced sufficient myocardial anoxemia to have precipitated a myocardial infarction. We are all familiar with patients with pernicious anemia who have angina when their red cell count is very low and are subsequently free of any anginal pain once their blood count returns to normal.

DR. ALEXANDER: This patient had a small kidney on one side and he died in uremia. Dr. Schroeder, would you comment on this aspect of his illness?

DR. HENRY A. SCHROEDER: From the results of the pyelograms it seems that the patient had only one functioning kidney. It occurred to me that if only one kidney was functioning the deposition of hemosiderin in the tubules might be greatly increased and therefore lead to renal damage more quickly than would be the case had the patient had two normal kidneys originally. The development of cardiac failure adversely affects nitrogen retention, and, in a kidney which is on the verge of failure anyway, may lead to definite azotemia. I believe the patient probably had nephrosclerosis, perhaps a great deal more than would have been predicted on the basis of his blood pressure and the size of his heart. His blood pressure may have been lowered because of the anemia.

DR. WOOD: Dr. Schroeder, do you think that this patient had unilateral pyelonephritis leading to hypertension? Why was the right kidney smaller?

DR. SCHROEDER: I cannot answer your question on the basis of the data at hand. Statistics from the Mayo Clinic indicate that hypertension is no more common in patients with organic renal diseases than in the rest of the population. There are, how-

ever, some cases on record in which removal of one diseased kidney has been followed by prolonged improvement in the level of the patient's blood pressure. It is my own belief, from a study of factors contributing to the onset of hypertension, that in predisposed individuals pyelonephritis may initiate and maintain hypertension indistinguishable from the so-called essential type and, furthermore, that this sequence occurs more often than is commonly appreciated.

DR. ALEXANDER: Dr. Kenamore, do you believe that the severe abdominal pain could have been due to a peptic ulcer?

DR. BRUCE D. KENAMORE: I thought that perhaps thrombosis of the splenic vein had given rise to the pain; it may be accompanied by signs of associated peritoneal irritation.

DR. ALEXANDER: Does it not require a rather large clot to thrombose the splenic vein?

DR. WINTROBE: I think it is perhaps more likely that the patient had a splenic infarct with resultant peritoneal irritation.

DR. ALEXANDER: Dr. Schroeder, do you think there will be specific tubular damage due to hemosiderin?

DR. SCHROEDER: I read in Dr. Wintrobe's book that hemosiderin is deposited in the tubules in this disease.

DR. ALEXANDER: Dr. Moore, do you agree that the patient had intravascular thromboses?

DR. C. V. MOORE: I think so, but I still believe that he had paroxysmal nocturnal hemoglobinuria.

DR. WOOD: I am still interested in knowing what lesion will be found in the right kidney. It did not function properly and I believe the pathologists will be able to tell us why.

DR. ALEXANDER: You believe that it probably represents the end result of pyelonephritis, do you not?

DR. WOOD: I think so.

DR. ROBERT J. GLASER: This man had an aortic diastolic murmur on his first admission. I wonder if Dr. Wintrobe would comment on the occurrence of aortic dia-

stolic murmurs in severe anemia. We have not infrequently heard mitral diastolic murmurs under such circumstances but the others have been rather rare in our experience.

DR. WINTROBE: I agree that hemic aortic diastolic murmurs are quite unusual but I think that one must be cautious in commenting about the murmurs which are heard in association with hemolytic anemia. I think all of us have had the experience of listening to the hearts of patients with sickle cell anemia and have been convinced that there were valvular lesions, only to learn subsequently from the pathologists that no valvular defects were present.

DR. GLASER: You would not be surprised if there was no aortic lesion at all?

DR. WINTROBE: I would not.

DR. ALEXANDER: Would you be surprised, Dr. Glaser?

DR. GLASER: No.

DR. SCHROEDER: This patient had hypertension and aortic diastolic murmurs may occur as a result of hypertension.

DR. ALEXANDER: In conclusion, it seems that we agree that this patient had hypertensive cardiovascular disease and arteriolar nephrosclerosis. Myocardial infarction due to the combination of coronary sclerosis and severe anemia has been proposed. The patient likewise certainly had hemoglobinuria, and the evidence seems to favor the diagnosis of paroxysmal nocturnal hemoglobinuria although there are various factors including the patient's age which are somewhat against that diagnosis. A splenic infarct may well have explained his abdominal pain and the possibility of intravascular thromboses has likewise been mentioned.

Clinical Diagnoses: Paroxysmal nocturnal hemoglobinuria; hypertensive cardiovascular disease; arteriolar nephrosclerosis; myocardial infarction; infarct of the spleen; intravascular thromboses.

PATHOLOGIC DISCUSSION

DR. FRANK TOWNSEND: At the time of autopsy the principal external finding was

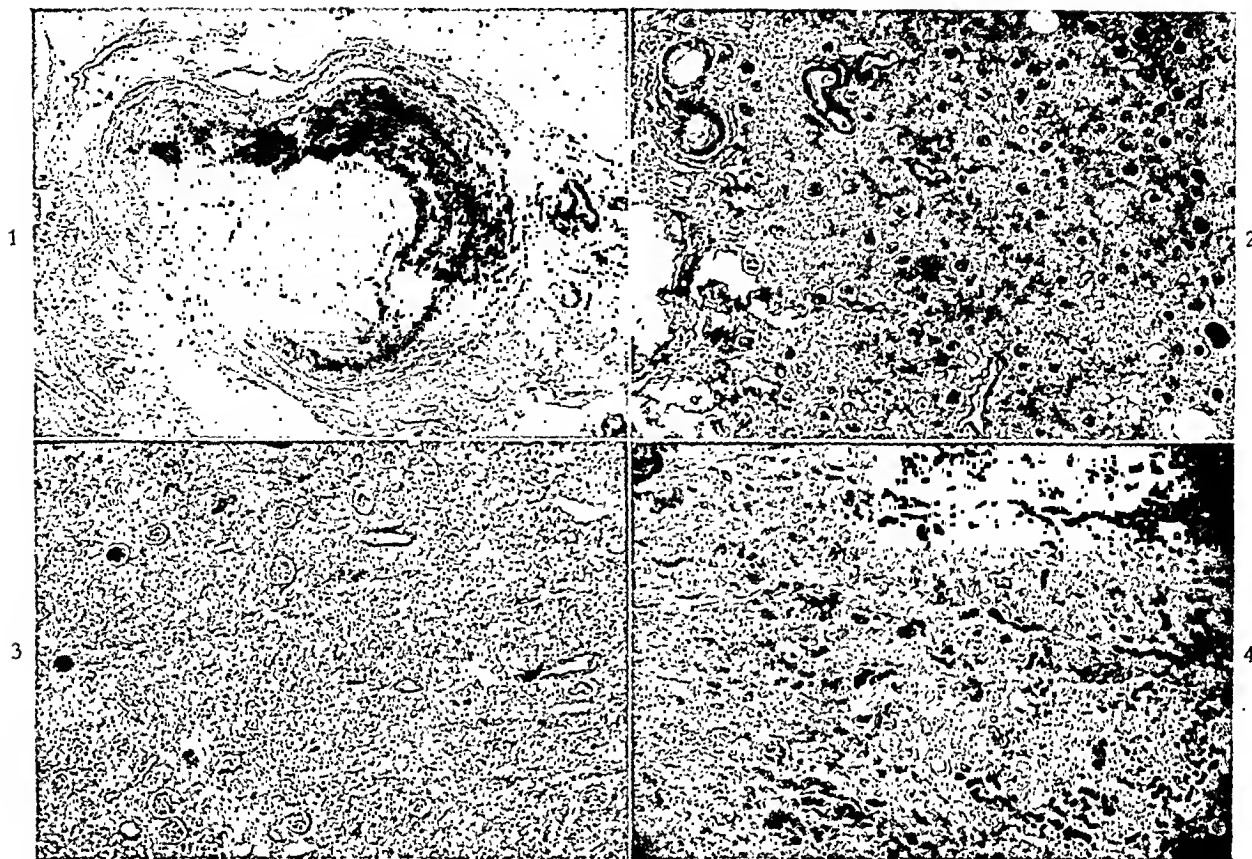


FIG. 1. Section of the right renal artery showing an organized, recanalized thrombus in the lumen.

FIG. 2. Section of the cortex of the right kidney through the atrophic portion. Note the degree of fibrosis and hemosiderosis.

FIG. 3. Section of the cortex of the left kidney. Note that the glomeruli are larger in size and that the degree of fibrosis and atrophy is less than is seen in Figure 2.

FIG. 4. Section of the cortex stained for iron. Note the large amount of hemosiderin in the epithelium of the convoluted tubules and of the ascending loops of Henle.

the yellow color of the skin. On opening the thorax examination of the heart revealed the presence of a fibrinous pericarditis. One hundred thirty-five cc. of serofibrinous fluid were present in the pericardial cavity. The heart was enlarged, weighing 610 Gm. There was moderate sclerosis of the coronary arteries, especially of the anterior descending branch of the left coronary artery, which at one point was practically occluded by an arteriosclerotic plaque. In the septum there was an area of greyish tissue in which depressed, red, irregular foci were seen; it was believed that the changes represented a healing infarct. The only other point of interest in the heart was that there were subendocardial ecchymoses in the right atrium. No valvular abnormalities were present. The aorta was moderately sclerotic.

The lungs weighed 1,970 Gm. The right pleural cavity contained no fluid but in the left cavity 400 cc. of serous fluid were present. Most of the right pleural cavity was obliterated by fibrous adhesions. In the mucosa of the trachea and bronchi, which was yellowish-white in color, there were many small ulcers. The trachea and bronchi were filled with bloody, mucoid material. The periphery of the lungs was firm.

One hundred cc. of serous fluid were present in the peritoneal cavity. The left kidney weighed 316 Gm. and the outstanding feature in the gross was its extremely brown color. On cut surface differentiation of the cortex and medullary portions revealed them to be of normal proportions; in the renal pelvis there was a reddish area 1 cm. diameter. The right kidney weighed

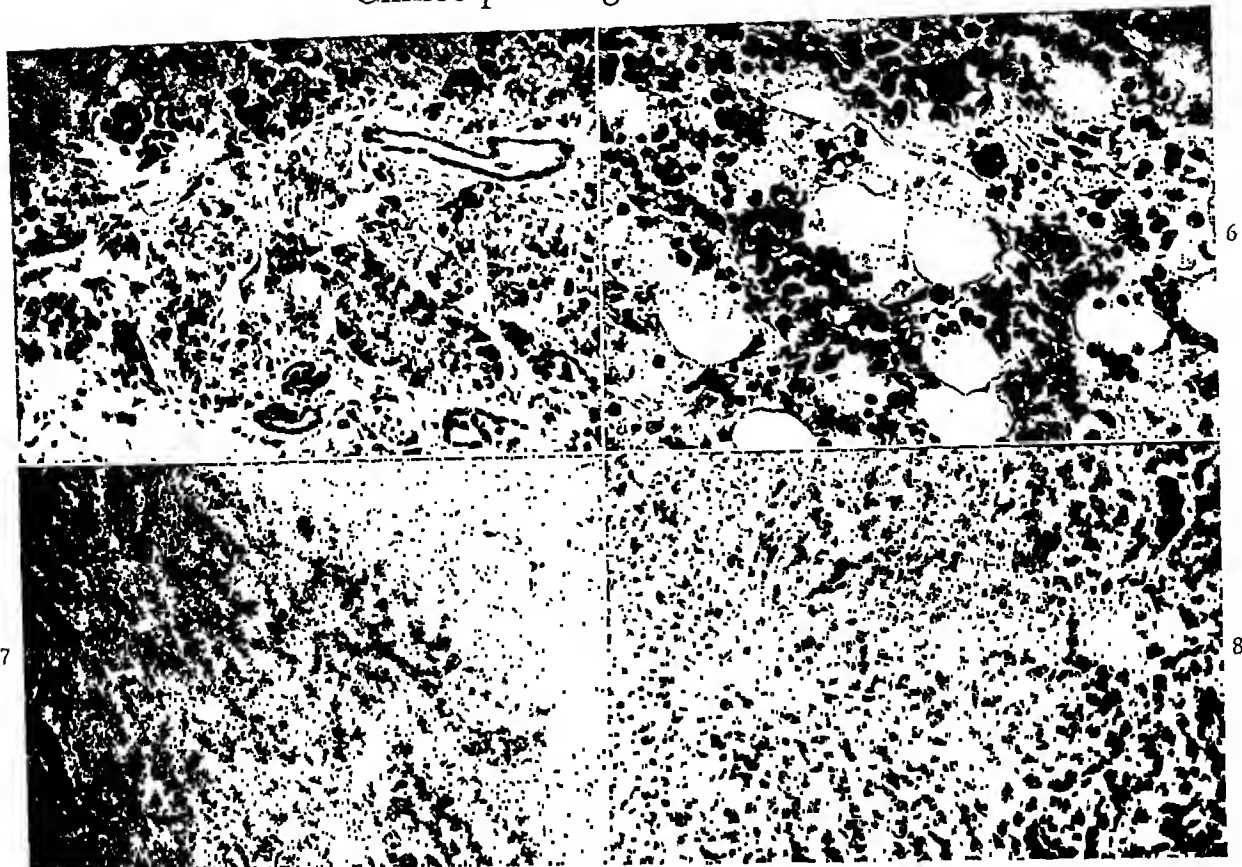


FIG. 5. A higher power view which shows in better detail the changes described in the previous section.

FIG. 6. Section of the femoral marrow showing hyperplasia, particularly of the erythrocytic elements.

FIG. 7. Section of the spleen showing the marked hemosiderosis.

FIG. 8. Section of the liver which shows the changes of chronic passive congestion.

95 Gm. There was an old organized thrombus within the lumen of the main right renal artery which was completely occluded, but an aberrant renal artery, supplying the upper pole of the kidney, was patent. There was a definite line of demarcation between the upper and lower portions of the kidney. The tissue in the upper one-third appeared much as that in the left kidney, whereas the lower two-thirds of the right kidney had lost its characteristic appearance. The pancreas weighed 210 Gm. and appeared edematous. The spleen was enlarged, weighing 240 Gm. On examination the outer surface had depressed areas and on cut surface numerous grey areas were seen; others were red and hemorrhagic in appearance. Between these foci, which were interpreted as infarcts, there were areas of tissue which appeared normal except for their brown color. There were fibrinous and fibrous adhesions between the

spleen and the omentum and diaphragm. The liver weighed 2,850 Gm. and the outer surface was not remarkable. On gross examination of the cut surface the only change from the normal was a slight increase in blood. There were superficial erosions of the mucosa in the lower portion of the esophagus. The remainder of the gastrointestinal tract was normal. The bone marrow was red and appeared hemorrhagic.

DR. MARGARET G. SMITH: The first section (Fig. 1) is that of the organized and recanalized thrombus in the right renal artery. Most of the lumen is occluded but the degree of organization and recanalization indicates that the thrombus is quite old. The orifice of the artery was nearly occluded by an arteriosclerotic plaque and it is probable that the thrombus within the vessel arose on that basis. In Figure 2 a section of the cortex of the atrophic part of the right kidney is seen. As Dr. Townsend

has told you approximately two-thirds of this kidney was atrophic. The glomeruli are small and fibrotic, the tubules throughout the cortex are atrophic and there is an increase in the interstitial connective tissue. A large amount of hemosiderin is seen in the atrophic tubules and also in the interstitial connective tissue. Most of the deeply stained areas in the section represent hemosiderin. The next section (Fig. 3) is from the cortex of the left kidney. In comparison with the section from the right kidney the glomeruli are definitely larger. There is some interstitial fibrosis and atrophy of the tubules but much less than was present in the atrophic part of the right kidney. In another section thickening of the walls of the arterioles was seen. In addition there was fibrous thickening of the glomerular capsules and thickening of the basement membranes of the capillaries in the glomerular tufts. Atrophy of the tubules, which is apparent, may be explained on the basis of arteriosclerosis, but one must consider also the possibility that some of this damage may have been caused by the large accumulation of iron which is seen in the tubular epithelium. Figure 4 shows a section of the cortex stained for iron. There is a great amount of hemosiderin in the epithelium of the convoluted tubules and of the ascending loops of Henle; atrophy of the tubules and interstitial fibrosis may also be seen. In another section a few casts having the staining characteristics of hemoglobin were present. Hemoglobin casts were found in the convoluted tubules of the loops of Henle, and there were some hyaline casts in the distal convoluted tubules. Figure 5 shows the large amount of hemosiderin in the epithelium of the convoluted tubules and the degeneration of the epithelium. There was no necrosis of the renal arterioles such as is seen in malignant hypertension. However, in a section of the pancreas some of the arterioles did show necrosis. There were some foci of necrosis in the pancreatic tissue and, occasionally, fibrin thrombi were seen in the capillaries. There was edema of the connective tissue about the

pancreas with deposition of fibrin. These changes in the pancreas may have accounted for some of the patient's pain in the later days of his illness, but it seems more likely that the pathologic changes in the spleen were responsible for the pain which was present for three weeks. A section of the femoral marrow showing hyperplasia is seen in Figure 6; the hyperplasia chiefly involves the erythrocytic elements. The capillaries are dilated and filled with red blood cells. In a section of the spleen (Fig. 7) there is a large amount of hemosiderin within phagocytic cells between the sinusoids; some of the phagocytes contain both red blood cells and granules of hemosiderin. In other sections of the spleen there were organized and recent thrombi in both arterics and veins. Arteriosclerosis was not marked in the splenic arteries and does not offer a satisfactory explanation for the formation of thrombi. In a section of the liver (Fig. 8) there is loss of liver cells at the center of the lobule. The sinusoids are dilated. These changes are interpreted as being those of long standing chronic passive congestion. The Kupfer cells, which cannot be seen distinctly in the section, contain red blood cells and a small amount of hemosiderin.

A section of the anterior descending branch of the left coronary artery revealed almost complete occlusions of the lumen by an arteriosclerotic plaque; the sclerotic changes in the rest of the coronary arteries, as Dr. Townsend stated, were moderate. Sections of the myocardium showed changes characteristic of healing and recent infarcts. In the areas of recent infarction there was necrosis of muscle fibers with absence of nuclei and striations. In the older part of the infarct there were no muscle fibers, only vascular connective tissue having thin collagen fibrils. Because of the vascularity of the connective tissue and the lack of dense collagen fibers, it was thought that that part of the infarct was a few weeks old.

In summary, the major findings included arteriosclerosis of the coronary arteries with healing and recent infarcts of the myocar-

dium. There was occlusion of the right renal artery with atrophy of two-thirds of that kidney. Moderate arteriolar nephrosclerosis was present. It is possible that the occlusion of the renal artery with resulting renal ischemia was of importance in the development of hypertension. The heart was hypertrophied and dilated, and fibrinous pericarditis, a manifestation of uremia, was present. There was much hemosiderin in the epithelium of the convoluted tubules and of the loops of Henle; degenerative changes were present in the epithelium. There were hemoglobin casts in the collecting tubules. Degenerative changes in the renal tubules are not reported in most cases of paroxysmal hemoglobinuria, but it is possible that they occurred in this patient because renal damage due to arteriolosclerosis was also present. Erythrophagocytosis and deposits of hemosiderin in the spleen are likewise not reported in paroxysmal hemoglobinuria, but in this instance can be related to the blood transfusions which the patient received. The abdominal pain may be explained on the basis of peritoneal irritation arising as a result of recent infarcts in the spleen.

Anatomic Diagnosis: Arteriosclerosis of the coronary arteries, moderate of the right,

advanced of the left; healing and recent infarcts of the interventricular septum; arteriosclerosis of the thoracic and abdominal aorta, moderate, with plaque narrowing orifice of right renal artery, of the splenic artery, moderate; organized thrombus in the right renal artery; aberrant artery to superior pole of right kidney; atrophy of the inferior two-thirds of right kidney; arteriolar nephrosclerosis, moderate; hypertrophy and dilatation of the heart (610 Gm.); chronic passive congestion of the liver; hydrothorax, left (400 cc.); serofibrinous pericarditis (150 cc.); necrosis of arterioles and small arteries in pancreas; fibrin thrombi in capillaries in pancreas; foci of necrosis of pancreas; acute necrotizing bronchitis and tracheitis; hemosiderosis of the kidneys, advanced; congestion and focal hemorrhage of the bone marrow; organized and recent thrombi in veins and arteries in the spleen; healing and recent infarcts in the spleen; hemosiderosis of spleen, moderate; splenomegaly (440 Gm.); erythrophagocytosis in liver, spleen, bone marrow and lymph nodes (history of blood transfusions).

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Traumatic Rupture of the Aortic Valve*

R. W. KISSANE, M.D., R. A. KOONS, M.D. and THOMAS E. CLARK, M.D.

Columbus, Ohio

A REVIEW of the literature up to the year 1928 by Howard¹ revealed 113 cases of ruptured aortic valve as the result of muscular effort or trauma and that Plenderleath² reported the first case in 1830. There were fourteen of these cases proven by autopsy to be due to contusion and a search of the literature up to the present time has failed to reveal any additional cases. The first of the two cases discussed here was previously reported³ but is reviewed for comparison with the second case.

CASE REPORTS

CASE 1. K. S., a single white male, aged twenty-two years, with a normal family and past history was injured in an explosion which completely buried him by stone and débris. There were numerous fractures and lacerations of the entire body including a fracture of the sternum with discoloration of the entire anterior and posterior surface of the thorax due to contusions. When he regained consciousness he complained of a crushing sensation in his left chest associated with severe dyspnea. After eight months he had recovered from the external injuries but during this time he continued to complain of the crushing sensation in the left chest, of moderate dyspnea which became severe on exertion, of moderate palpitation on exertion, frequent attacks of syncope, severe dizziness and anxiety with fear of impending death. During the attacks of severe dizziness and syncope he would first become pale followed by cyanosis of the lips and fingernails. Fourteen months after the accident he had pain in the right kidney region and signs of congestive heart failure which caused his death two days later. An examination a year before the accident revealed this man to be normal in

every respect. Another examination two days before death showed engorgement of the neck veins, swinging of the carotid arteries and a pulsation in the suprasternal notch. The apex beat was not palpable and the cardiac dullness in the fifth interspace was 10 cm. to the left and in the fourth interspace 5 cm. to the right of the mid-sternal line. There was a loud, rough, diastolic murmur heard at the base of the heart and along the left border of the sternum, with the maximum intensity at the aortic area. There was also a slight roughness of the first sound at the apex. The rhythm of the heart was regular and the rate was 96. The pulse was of the Corrigan type with a 110 mm. systolic and 20 mm. diastolic blood pressure. The liver was at the costal margin but there were many moist râles in the bases of both lungs. The urine contained a large amount of albumin, no sugar but many red blood and pus cells. The blood count was 80 per cent hemoglobin, red blood count 4,320,000 and the white blood count 15,200. The orthodiagram showed a transverse diameter of the heart of 15.5 cm. The Wassermann reaction was negative. The diagnosis was traumatic heart disease, ruptured aortic valve, aortic insufficiency, myocardial insufficiency and congestive heart failure with possible embolism of the right kidney.

Autopsy results were as follows: The sternum was separated at the synchondrosis sternalis between the manubrium and the body of the sternum in such a manner that it was easily hinged outward and the periosteal fibers supporting this synchondrosis were relaxed so that the body of the sternum was easily displaced backward into the mediastinum to the extent that it overrode the lower margin of the manubrium sterni. The myocardium of the left ventricle was of the usual thickness and of good consistency. The cusps of the aortic valve were

* From the Cardiological Departments of the Ohio State University College of Medicine and White Cross Hospital, Columbus, Ohio.

ragged and partially covered with precipitated blood. There was a transverse slit just below the margin of the left posterior cusp, the right posterior cusp was irregularly torn, fragmented and infiltrated with blood and the anterior cusp was also extensively torn. There was no gross evidence of any inflammatory reaction. The valve was entirely incompetent. At the base of the anterior cusp the adjacent myocardium and the subpericardial adipose tissue was discolored a dark, reddish brown by an old hemorrhagic infiltration. The remainder of the heart was normal. The lungs contained a moderate amount of edematous fluid and diffuse congestion. There was a large area of infarction in the right kidney.

Microscopic sections of the ruptured cusps of the aortic valve showed a thin fibrous structure and on both surfaces of the valve a precipitate of hemorrhagic material. Immediately adjacent to the fibrous tissue of the valve was a thin layer of plasma cells and a small amount of fibrin while external to this, red blood cells were arranged in a granular material simulating the precipitation type of blood clot. The sections through the myocardium and subpericardial tissue at the base of the aortic valve showed infiltration with round cell and non-nucleated cells and throughout the entire section there was an extensive deposition of blood pigment. Other sections of the myocardium were normal. In the lungs the alveolar spaces were filled with edematous fluid in which there were a few red blood cells and many heart failure cells. The sections of the right kidney through the area of infarction showed a complete destruction of the kidney tissue and replacement with a hyalinized homogeneous material.

Diagnosis: Rupture of the aortic valve, hemorrhagic infiltration about the base of the aortic valve, separation and dislocation of the sternal synchondrosis, bilateral congestion, edema of the lungs and infarction of the right kidney.

CASE 11. L. B., a married white male carpenter, age fifty-eight, with an irrelevant history except for influenza in 1918 and a herniotomy in 1931, was injured in May, 1937. While running, he had jumped over a concrete form and a lath flew between his legs which threw him to the soft muddy ground in such a manner that he struck his chest and abdomen with his arms extended. He immediately arose and walked to his automobile when he felt and heard a thrill or purring in his upper chest and noticed

soreness in the sternal region. As he drove home he continued to hear this peculiar sound and developed some palpitation, tachycardia and slight dyspnea. That evening his wife was alarmed when she heard this purring-like noise at a distance of three feet from the patient. An examination revealed engorgement of the neck veins with swinging carotid arteries. The apex beat was in the fifth interspace 7.5 cm. to the left of the mid-sternal line and there was a pronounced thrill felt over the midsternum and in the aortic area. The cardiac dullness in the fifth interspace was 8 cm. third interspace 4.5 cm. to the left and in the fourth interspace 4.5 cm. to the right of the mid-sternal line. A loud, rough, musical diastolic murmur was heard at the aortic area. This murmur together with a soft systolic murmur was also heard at the mitral area. The rhythm was regular with an occasional premature contraction, the pulse rate was 72, Corrigan in character, and there was a definite capillary pulsation. The liver was at the costal margin and tender, the blood pressure was 130 mm. systolic with a diastolic of 0 mm., the blood Wassermann reaction was 4 plus; Kolmer's test was 3 plus, Kahn's test showed 4 plus and a non-protein nitrogen count was 44 mg. Under the orthodiagram the heart was normal in size and contour and in the second oblique position there was a slightly abnormal pulsation of the first part of the aorta. The electrocardiogram was normal with left axis deviation, the vital capacity was 72 per cent and the venous pressure was 40 mm. of water. A diagnosis was made of traumatic heart disease with traumatic rupture of the aortic valve and aortic insufficiency. This man continued to work with no marked changes except a slight increase in dyspnea and some decrease in vital capacity, until four months later when the transverse diameter of the heart under the orthodiagram was observed as 15 cm. After nine months he had severe substernal pain referred through to the left scapula followed by a marked cough, severe dyspnea and orthopnea which required oxygen and a narcotic for relief. One month later the transverse diameter of the heart was 17.2 cm. and the electrocardiogram showed a depression of the RST segment in lead 1 with a low take-off and a negative T wave, a slightly negative T2 and an upright T3 with slightly elevated RST segment, in addition to an increased left axis deviation. The blood pressure at this time was 180 mm. systolic, 0 mm. diastolic and the heart rhythm was regular with a

rate of 100. He had severe chest pains every two to three days which would sometimes last for forty-eight hours and he developed definite attacks of paroxysmal nocturnal dyspnea. After eighteen months the transverse diameter of the heart was 18.4 cm. and the blood pressure was 220 mm. systolic, 0 mm. diastolic. The pain and nocturnal dyspnea were even more severe with occasional signs of pulmonary edema and slight edema of the ankles. These symptoms were benefited somewhat by the use of oxygen especially during the night. A month later he had an acute attack of pulmonary edema with marked congestive heart failure; however, he improved under treatment but it was necessary now to give a mercurial diuretic every two or three days to prevent the advance of congestive heart failure. From twenty-two months on the patient was almost continuously in congestive heart failure and required a narcotic every few hours for relief from the terrific pain in his chest. Then, after twenty-seven months incisions were made on the lateral surfaces of both legs just above the ankles in order to drain the edema fluid which could not be controlled by the mercurial diuretics. This gave him some relief for a short time and reduced the edema and ascites but shortly after this he died, just two years and three months after the injury.

Autopsy findings were as follows: The general description of the body was an emaciated, white man sixty years of age with a small surgical incision on either side of both ankles. The thorax was opened revealing an enormously enlarged cardiac area which measured 19 cm. in the widest transverse diameter. The right border extended approximately 1 cm. beyond the right sternal margin while the apex was against the left thoracic wall. The left lung was confined above the enlarged heart and the right lung was completely bound down by adhesions. The pericardial sac contained the usual amount of clear, amber fluid. The enormously enlarged heart measured 18.5 cm. in the widest transverse diameter and the right auricle was engorged with blood. The pulmonary and tricuspid valves were normal but slightly widened. The aorta was smooth and pliable, except for an occasional area of atherosclerosis. The aortic valve presented an unusual picture in that there was a splitting and separation of the commissures between the right and left posterior cusps resulting in a sagging, free, flap-like part of these cusps, which moved with equal ease either upward into the aorta or downward into the

left ventricle and produced a definite, permanent opening along the line of the separated commissures. The anterior cusp was normal. The two cusps of the valve which were involved by this separation of the commissures were unusually smooth, fibrous in character with an average of 1 or 2 mm. in thickness. The mitral valve was normal and the myocardium of both right and left ventricles was extremely hypertrophied. In the left lung there was a small amount of congestion and edema and the right lung, which was firmly adherent to the chest wall, diaphragm and mediastinum, showed an encapsulated empyema between the lower lobe and diaphragm, with approximately 4 ounces of thin, greenish, foul-smelling pus and also an adjacent abscess which measured 4 cm. in diameter. The remainder of the lung was moderately congested but not consolidated. The liver was 4 cm. below the right costal margin, dark in color, and moderately congested. All other structures and organs were normal.

Microscopic sections showed an acute bronchitis in the lungs, partial atelectasis, some edema, numerous heart failure cells, advanced pulmonary arteriosclerosis and in the lower lobe of the right lung a dense replacement fibrosis of the pleura, passing through a zone of granulation tissue into a purulent exudate lining the encapsulated empyema. In the sections of the myocardium from both ventricles there was marked hypertrophy of the individual cells with an occasional area of granular degeneration. Sections through the traumatic commissure of the aortic valve showed hypertrophy of the myocardium at the base of the valve with the myocardial cells and their nuclei quite large. The blood vessels within the myocardium at this point were somewhat thickened. Immediately adjacent to the commissure there was some granular degeneration of the myocardial cells and the commissure itself showed an acellular fibrosis with a few round cells distributed through the fibrous tissue. The surface was covered with a thin layer of endothelium. The myocardium from other portions of the left ventricle was extensively hypertrophied with occasional small areas of brown atrophy. The aorta above the valve had an intact surface and intima but the adventitia showed a few round cell accumulations which extended into the media. The vaso vasora, however, were normal and the round cell infiltration was not associated with these blood vessels but appeared diffusely in the medial and adventitial layers. Also within

the media there were areas of hyalinized fibrosis and limited areas of degeneration and calcification. The injured leaflets of the aortic valve were partly covered with endothelium and the entire valve was thickened with an acellular connective tissue which was completely avascular. There was no evidence of recent or old hemorrhage, except in very occasional areas at the base of the valve where there were a few granulation type capillaries, about which there were a few monocyte and round cells and a small amount of pigment.

Diagnosis: A partly healed traumatic rupture and separation of the commissures between the posterior cusps of the aortic valve, progressive fibrosis and relaxation of the cusps of the aortic valve, permanent aortic insufficiency, myocardial hypertrophy and granular degeneration, chronically suppurative empyema and lung abscess of the right lung, acute bronchitis, edema, heart failure cells, partial atelectasis, advanced pulmonary sclerosis of the lungs and congestion of the liver.

COMMENTS

Of the 113 cases reported by Howard there were only fourteen proven cases of patients with no evidence of syphilis and in only thirteen out of forty-eight autopsies of the entire series was the aortic valve reported absolutely normal. This was true, however, in 44 per cent of patients in the traumatic group as against only 23 per cent of those in the strain group. In the second case reported here, while there was some syphilitic aortitis, there was no evidence at autopsy of syphilitic involvement of the aortic valve which could weaken the cusps causing spontaneous rupture. It was previously thought that the traumatic lesion was the result of a fall from a height and did not occur following such trauma as burial under an avalanche of debris. However, case 1 and others have lately demonstrated the fallaciousness of the view that rupture could be due only to bursting and that the gradual pressure applied by burying was not sufficient to cause this lesion. Bernstein⁴ made the interesting observation that tears of the aortic valve cusps are only partial because as soon as the rupture occurs the pressure is relieved, preventing

further tearing. External injury such as falling against the anterior chest wall or burial under debris causes the column of blood in the aorta during cardiac diastole to increase suddenly to the degree that the wall of the aorta or cusps of the closed aortic valve tear. The older writers believed that this type of rupture usually occurred in only one cusp; however, in both of the cases presented more than one cusp was injured.

Traumatic valvular rupture occurs in both normal and diseased valves but great care should be taken in differentiating the latter from spontaneous rupture, which most frequently occurs without any injury or muscular activity and is more frequently confused with injury produced by overexertion. The aortic valve is most frequently injured by contusion. The tears of the cusps heal with the formation of scar tissue, especially when the tear is along the base or commissure of the leaflet. Besides fragmentation of the free edge of the cusp, rupture of the chordae tendineae and papillary muscles also occurs. These injuries, when the result of contusion, are usually associated with other traumatic lesions. Healing of the fragmented parts of the valve cusps results in thickening which tends to smooth off the rough edges. The thickening thus caused produces stenosis and a certain degree of insufficiency. Frequently the fragments will grow together or become attached to the wall of the ventricle but it appears that complete healing with obliteration of the entire opening does not occur.

The absence of immediate severe symptoms following injury or exertion is strong evidence of a spontaneous rupture rather than a traumatic tear. The most characteristic and immediate symptom in the latter condition is acute and frequently agonizing chest pain of a sharp, tearing character located substernally and across the upper chest. This pain radiates up to the neck and down the left arm or through to the back between the shoulder blades, and may be accompanied by *angor animi*

or sense of impending death such as is associated with angina pectoris and coronary artery occlusion. Severe dizziness, vertigo with faintness and syncope are early symptoms. There is also an early development of rather severe dyspnea and palpitation with a sensation of roaring and pulsation in the chest, neck and ears. The murmur frequently can be heard not only by the patient but by others at quite a distance. This peculiar phenomenon has been described by various patients as "the cooing of a dove";^{5,6} "rumbling, rustling noise";⁷ "a humming noise";⁸ "the croaking of a frog";⁹ "a whistling noise";¹⁰ "a buzzing in the chest";^{11,12} "musical murmur or thrill";^{13,1} "rattle in the head";¹⁴ "whirring noise";¹⁵ or a "purring." Of course, all the classic signs and symptoms of aortic insufficiency also develop immediately.

Associated with a diastolic murmur, loudest at the base of the heart, is a systolic murmur. The hypothesis of Foster¹⁶ is that this is due to vibrations of the valve cusps floating in the blood stream. He adds that if this is true, the systolic murmur has a certain prognostic importance and also that when the murmur spreads towards the apex it is due to insufficiency of the left aortic segment; if it spreads toward the ensiform cartilage, it is due to insufficiency from a lesion of the right and posterior cusps. He describes the diastolic murmur as of a special blowing and flapping character. According to Strassman¹⁷ it is often longer, of a peculiar tone and more intensive than the soft murmur of aortic regurgitation due to endocarditis. In the review by Howard¹ the murmur was described as, "harsh or intense," in nine cases, "prolonged and loud, gushing, rumbling, creaking, flapping, rough and flapping, rasping or piping," each in one case. In six cases it was described as musical, without other qualification, while in nine other cases the musical quality was modified by such terms as "sibilant" in two cases, "vibrating, tone like the vibration of a string, piping, buzzing, purring, like a torn sail" and "siren-like" each in one case.

The marked thrill frequently associated with this murmur, it should be remembered, is caused also by traumatic rupture of the septum. Frequently total disability occurred almost immediately but in a few instances light work could be continued for a short time. The disability was probably due to sudden regurgitation of blood into the left ventricle before adequate compensatory hypertrophy could take place. The two cases of traumatic rupture of the aortic valve described in this report did not show acute dilatation but steady progressive enlargement of the left ventricle. The definite healing tendency of rupture of the aortic valve accounts for the favorable short-term prognosis; but the resulting aortic insufficiency progresses in the usual manner and at a much more rapid rate than when caused by disease, with the same ultimately fatal result. Barie¹⁸ believed that perhaps the prognosis was more grave when the rupture interfered with maintaining diastolic blood pressure at the coronary opening, thus decreasing coronary filling. However, rupture of any cusp at any place would have the same result depending upon the degree of insufficiency produced. There may be immediate fatal syncope or gradually developing circulatory failure; the prognosis depending primarily upon the size of the defect and secondarily upon the myocardial efficiency.

The duration of life was given by Howard¹ for thirteen of the proven cases. In one patient death was immediate; in another in a few hours; in a third but two hours intervened and in a fourth the patient survived three days. On the other hand, one patient survived ten years and another eleven years and one month which made a mean duration for the group of forty months for those that survived the immediate effects of the trauma. Both the patients described here died in a considerably shorter period of time.

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Esophageal Hiatus Hernia^{*}

MAURICE M. POMERANZ, M.D. and MILTON E. GOLDSTONE, M.D.

New York, New York

WHILE the problem of roentgenographic diagnosis of diaphragmatic hernias has been clarified in recent years, considerable interest is still occasioned by the unusual forms which the anomaly may take and the great discrepancy between clinical assumptions and roentgen data. Because many of these hernias are often entirely asymptomatic they may be discovered only incidentally at operation or postmortem examination. Those which produce symptoms do so either immediately after birth or remain undiscovered until late in life.

The following report is that of an esophageal hiatus hernia which was revealed on routine roentgen ray examination. Because of the bizarre character of the lesion it was considered of sufficient interest to warrant further investigation.

CASE REPORT

A woman, married, aged forty-seven, was admitted to the hospital in September, 1945, complaining of epigastric pain associated with weakness and dizziness. Her medical history was irrelevant. The present illness began about seven to eight years before with vague epigastric distress unrelated to food but associated with heart burn and occasional vomiting. After a few years pain radiated to the right and posteriorly as well as to both shoulders. It was relieved somewhat by local application of heat, by lying on the left side or by leaning forward. During the past few years she experienced generalized abdominal distention relieved by local pressure. She complained of a constant sense of strain or discomfort in the epigastrium and lower part of the chest and lately suffered dizziness and weakness as well as dyspnea and palpitation on walking up one flight of stairs. There had been a gradual dietary intolerance

particularly to fried foods, eggs and apples. She had no bloody stools but occasionally vomited bright red, blood-tinged food particles. Her weight had remained stationary during the past year.

Physical examination revealed a well nourished middle-aged, white woman in no apparent distress. The head and neck were normal except for extreme tenderness in the right supraclavicular fossa. There were no palpable nodes. The heart and lungs were apparently negative. The liver was palpable six fingers below the costal margin and extended laterally to the iliac crest. It was hard, nodular and not tender. No other masses were felt. Generalized tenderness was noted in the epigastrium.

On fluoroscopic examination no abnormality was noted in the upper halves of the thorax. The left diaphragm was normal in position and excursion but the stomach bubble was not in its usual position. Loculations of gas were seen below the left diaphragm which appeared to be loops of intestine. Several abnormalities were present at the base of the right lung. A large ovoid, opaque mass lay adjacent to the right cardiophrenic sulcus. It was triangular with the hypotenuse directed obliquely from the middle of the diaphragm to about the level of the base of the heart. (Fig. 1.) The diaphragm could be traced from the right costophrenic sulcus medially for about 5 cm. where its outline was lost. In the center of this mass or density the stomach bubble was seen to the right of the midline. The shadow of the gas bubble overlapped the right lower angle of the heart and through it the pulsation of the right cardiac border could be observed. In the right oblique and lateral projections, the aforementioned mass could be seen lying posterior to the heart and occupying the right paravertebral area. The visualized part of the right diaphragm was clear and regular. The heart was normally placed and forcible pulsations were noted at its borders.

^{*} From the Department of Radiology, Hospital for Joint Diseases.



FIG. 1. Note obliquity of right diaphragm and triangular density in the cardiohepatic angle.

Administration of a small amount of barium mixture revealed the esophagus to be normal in size and shape. The opaque mixture was seen to descend to an area just above the orifice in the left leaf of the diaphragm where it turned sharply and passed posteriorly and upward to empty into what apparently was the cardia of the stomach lying above the upper border of the liver and to the right of the midline. (Fig. 2.) In the lateral projection the proximal part of the stomach was seen to lie posteriorly. It was "U-shaped," placed on its side with its upper arm above the level of the diaphragm, its lower arm below and its base directly to the right of the right paravertebral recess. (Fig. 3.) The barium mixture passed freely through the stomach and coursed downward and anteriorly through a narrowed channel which apparently was the duodenum or some part thereof. A small diverticulum was seen in the second part of the duodenum. The narrowed intestine passed downward into the pelvis where the mucosal pattern of the jejunum was identified. Roentgenograms confirmed the fluoroscopic diagnosis.

The roentgenoscopic and roentgenographic pictures presented a particularly



FIG. 2. The lower end of the esophagus deviates sharply to the right, posteriorly and upward to enter the cardiac extremity of the stomach. The major portion of the stomach is to the right of the midline. The pylorus and duodenum face to the left.

interesting problem in diagnosis and required a differentiation of the many varieties of diaphragmatic hernia in order to determine the category in an acceptable classification. Several classifications have been suggested usually based on the origin, structure or genesis of the defect. We have selected Harrington's¹ as representative and have modified it somewhat to conform to our conclusions.

CLASSIFICATION OF DIAPHRAGMATIC HERNIAS

1. Non-traumatic:

A. *Congenital*:

- (1) Foramen of Morgagni (subcosto-sternal)
- (2) Dome of diaphragm—absence of or gap left by incomplete hemidiaphragm; usually on the left side
- (3) Pleuroperitoneal (foramen of Bochdalek)
- (4) Esophageal hiatus:
 - (a) Congenital short esophagus
 - (b) Para-esophageal and esophageal hiatus hernias

B. *Acquired*:

- (1) Through an area of embryonic fusion
- (2) Through a congenital defect
- (3) Esophageal hiatus

2. Traumatic—of various categories, including severe crushing injuries, gun-

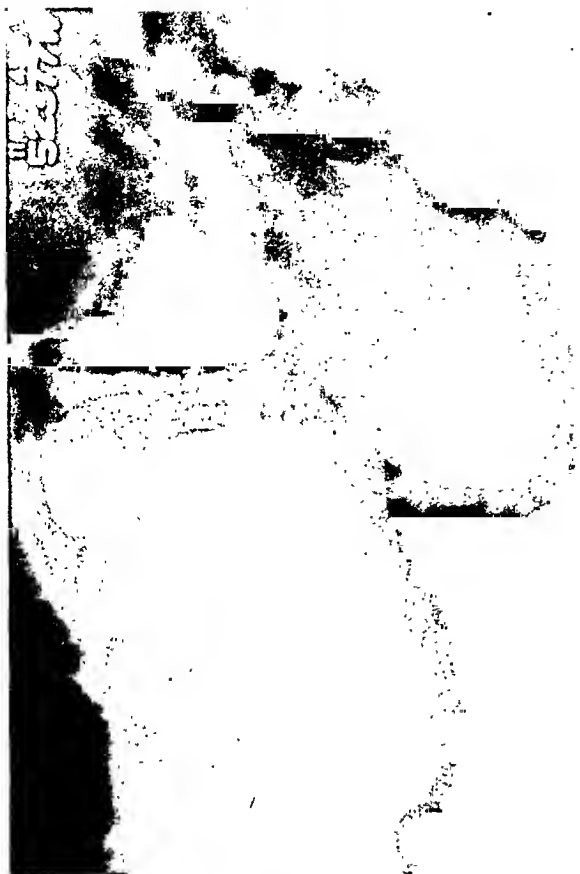


FIG. 3. Lateral view of the chest and abdomen showing the stomach in the posterior half of the thorax. Note that the lower pole of the stomach passes through the diaphragm and that the duodenum is anteriorly situated.

shot wounds, fracture of ribs, tear and rupture of subdiaphragmatic abscess.

We are concerned here solely with the non-traumatic group.

DIFFERENTIAL DIAGNOSIS

The subcostosternal hernia occurs through an opening in the diaphragm immediately beneath the right side of the sternum and right costal margin, through the foramen of Morgagni. Robbins,² in reporting an example of this variety, placed emphasis on its roentgenographic characteristics and especially on the shadow which lies close to the anterior thoracic wall. Thus, the site of hernias of this variety serves to eliminate our case from further consideration of this group.

Herniations through the dome of the diaphragm or through the pleuroperitoneal hiatus may be difficult to differentiate from

other varieties. Their site is significant to some extent, the first usually lying posteriorly and the second more laterally in the area of embryonic fusion of the diaphragmatic components. Accurate differentiation depends on the demonstration of the normal descent of the esophagus through the diaphragm, followed by herniation of the stomach through any of the aforesaid hiatuses. In our patient the esophagus, while of normal length, at no area passed through the diaphragm but instead moved posteriorly and upward to join the cardiac end of the stomach to the right of the midline. In a congenital short esophagus the stomach fails to descend below the diaphragm during embryonic development. It has been suggested that this form is not a true hiatus hernia but rather a congenital ectopia of the stomach caused by failure of descent during embryonic development.³

In our patient the esophagus was of normal length. In esophageal hiatus hernia the esophagus is seen to be of normal length and enters the stomach concentrically. This is by far the most common form of diaphragmatic hernia, the categories of which are described extensively in surgical literature. The roentgenologist frequently notes variations in size and position of this hernial pattern. It involves more than the upper part of the stomach. Less frequently found hernias are those which consist of either one-half or else the entire stomach, with or without other abdominal organs. In the first variety the lower end of the esophagus actually passes through the diaphragm and enters the stomach somewhat eccentrically. The herniated part of the stomach rests beside the esophagus in the posterior mediastinum. Harrington terms this variety "para-esophageal hiatus hernia." "In herniation of greater degree a sufficient part of the viscous passes through the orifice in such a manner as to drag the abdominal part and perhaps some of the lower segments of the esophagus. The roentgenographic signs then vary with the *degree of herniation* and may include: (1) gas bubbles above the level of the diaphragm; (2)

normal length of the esophagus; (3) the lower end of the esophagus, which may be redundant and tortuous because of upward displacement; (4) the lower end of the esophagus which may be displaced laterally; (5) fixation of the cardia above the diaphragm; (6) constriction of the cardia; (7) altered mobility of the diaphragm; and (8) displacement of the heart. Feldman⁴ points out that "in most instances the herniated portion lies to the left of the esophagus, somewhat posteriorly and as it increases in size approaches the midline, displacing the esophagus."

In our case of esophageal hiatus herniation the roentgenographic pattern revealed was as follows: (1) The stomach bubble was not in its usual position but above the diaphragm and posteriorly on the right side; (2) the esophagus descended to an area directly above the diaphragm and then passed sharply upward and posteriorly (Fig. 2); (3) the esophagus entered the cardiac end of the stomach above the diaphragm; (4) the stomach assumed a "U-shape" lying partly above and partly below the diaphragm; and (5) the duodenum passed from the right to the left, inclining downward and anteriorly through the diaphragm, its course beyond the pylorus apparently resting within the large hiatus.

CONCLUSIONS

In considering the bizarre roentgenographic pattern and the possible mechanism involved, it would seem that at one time the stomach rested in its normal position below the diaphragm. Furthermore, it is probable that for some unexplained reason the stomach migrated upward, pulling with it not only the esophagus at its cardiac end but also its peritoneal attachments, thus displacing the splenic flexure and adjacent parts of the colon. Beginning perhaps as a minor para-esophageal herniation the stomach continued its movement in such a manner as to enlarge the previous

hiatus to an extremely wide orifice extending from the site of the usual esophageal hiatus posteriorly and to the right. It was evident moreover that in its excursion the stomach rotated on its longitudinal axis with concurrent rotation on its transverse axis, coming finally to rest in the position it now occupied.

It is difficult to decide whether the primary defect was congenital or acquired. The absence of a history of trauma and of previous complaints, the possibility of an insidious onset and progression before reaching the overt clinical stage, caused doubt in regard to classification. Was a small para-esophageal hiatus hernia present at birth? Did it progress to this stage for forty years without inducing symptoms? Was there only a congenital defect of the hiatus wall at birth and were the clinical signs coincident with the onset of the process some eight years before? Were the stomach and its anatomic relations entirely normal until the onset of clinical signs eight years before?

After considering all the foregoing, we concluded that the correct classification of this anomaly probably was in the category of unusual, non-traumatic esophageal hiatus hernia.*

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*Since the completion of this report we were informed that the patient, while out of town, suddenly developed acute, upper abdominal distress and was admitted to a local hospital in a stuporous condition. The physical signs on admission suggested upper gastrointestinal obstruction. The patient never regained consciousness and died in about two days. Permission for postmortem examination was refused. So far as we could ascertain, no definite diagnosis was made. It is our impression that the cause of death was a volvulus of the stomach.

Western Society for Clinical Research

FIRST ANNUAL MEETING HELD IN SAN FRANCISCO

NOVEMBER 7 AND 8, 1947

CHOLESTEROL METABOLISM AND ITS RELATIONSHIP TO ATHEROSCLEROSIS, CORONARY ARTERY DISEASE, AND ARTERIOSCLEROSIS. *Lester M. Morrison, M.D.; Lillian Hall, M.D.; and Albert L. Chaney, Ph.D., Los Angeles, California.*

Blood serum cholesterol and ester levels in acute coronary thrombosis have been determined in some 500 cases at the Los Angeles County General Hospital.

These levels were compared to control cases in normals and in various diseases, such as hypothyroidism, cirrhosis of the liver, nephrosis, xanthomatosis, etc.

The cholesterol and ester levels were followed in coronary occlusion cases and in a normal series of controls.

These cholesterol and ester levels were then followed every six weeks in the Research Clinic after the administration of 6 Gm. of choline daily.

Cholesterol and ester levels were followed every six weeks in the Research Clinic—on high fat, low fat, high protein diets, and low protein diets to determine the influence of these diets on the cholesterol and ester blood levels.

SUMMARY

A consecutive unselected series of 200 patients with acute coronary occlusion was studied for blood cholesterol and cholesterol ester levels within forty-eight hours after hospital admission. In 68 per cent of seventy-five patients under sixty years of age with proven acute coronary occlusion hypercholesterolemia was present. In 52 per cent of 125 patients over sixty years of age with proven acute coronary occlusion a normal cholesterol level was found.

CONCLUSION

Coronary thrombosis in patients under the age of sixty is frequently associated with hyper-

cholesterolemia and disturbances of cholesterol metabolism.

PROTECTION AGAINST CYCLOPROPANE-EPINEPHRINE INDUCED CARDIAC ARRHYTHMIAS BY DIBENAMINE AND OTHER AGENTS. *Mark Nickerson, M.D.* (Introduced by H. H. Hecht, M.D., Salt Lake City.)

After induction of anesthesia with intravenous sodium pentothal (avc. 20 mg./Kg.), dogs were maintained on a 30 per cent cyclopropane-70 per cent O₂ mixture administered by endotracheal catheter with inflated cuff. After equilibration for thirty minutes, a standard challenge dose of 10 mg./Kg. epinephrine was injected intravenously in fifty seconds. Continuous standard-lead electrocardiograms were recorded during the period of epinephrine injection and until the cardiac rhythm returned to normal. Protective agents were administered ten to thirty minutes before the epinephrine.

About 25 per cent of unprotected animals developed ventricular fibrillation and the remainder showed long periods of ventricular extrasystoles and ventricular tachycardia. Dibenzamine (20 mg./Kg.) almost completely eliminated all irregularities leaving a sinus tachycardia as the only response to the epinephrine. Protection was equally effective when challenge doses of 100 and 1000 mg./Kg. were employed.

Prisol (20 mg./Kg.) was only slightly less effective than dibenzamine when tested with 10 mg./Kg. of epinephrine, but gave little protection against larger doses.

Demerol (10 mg./Kg.) and large doses of atropine sulfate (1 mg./Kg.) gave significant, but somewhat variable protection while quinidine sulfate (5 mg./Kg.), procaine hydrochloride (16 mg./Kg.) and ergotamine tartrate (0.25 mg./Kg.) had insignificant effects. Smaller

doses of atropine sulfate (0.1 mg./Kg.) and bilateral vagotomy did not protect, indicating that the protection afforded by massive doses of atropine is not due to its action in blocking vagal impulses.

No agent was found capable of restoring normal cardiac rhythm after ventricular fibrillation was established, even when given by intracardiac injection and accompanied by cardiac massage.

Dibenamine blocks most of the excitatory effects of epinephrine and sympathetic nerve impulses, but it has been shown not to sensitize animals to hemorrhagic shock. Its clinical use to prevent cardiac arrhythmias in patients under cyclopropane anesthesia is suggested.

ON THE USE OF AMMONIUM CHLORIDE BY VEIN IN RESISTANT EDEMA AND OLIGURIA; A PRELIMINARY REPORT. *Ferdinand Ripley Schemm, M.D., Great Falls, Montana.*

Ammonium chloride by vein was given fifty-two times to twenty patients in an effort to relieve edema or oliguria which had proven resistant to usual measures, 4.6 Gm. of ammonium chloride and 20 Gm. of dextrose in 1,000 cc. of distilled water appeared *in vitro* to give a maximum concentration of ammonium chloride without hemolysis and a maximum diuretic effect with a minimum of unpleasant reactions. The volume of the solution used was 1,000 cc. in eleven instances and 500 cc. in forty-one instances. One patient received eleven venoclyses of 500 cc. in four days.

The use of ammonium chloride was limited to two classes of patients; those who were obviously near the end of a long chronic illness and on whom the immediate effect of the drug on edema was observed, and those whose critical state depended chiefly on the edema or oliguria or anuria which had resisted other measures. In twelve cases, only one of them from the hopeful class, the ammonium chloride had no effect on the edema or oliguria. Severe reactions characterized by pallor, sweating and retching, were observed in five of these twelve cases, as well as in one of the eight cases that responded. In eight cases, four from the first class and four from the second class, the ammonium chloride appeared to be solely responsible for instituting a beneficial diuresis and/or the clearing of edema. The four from the hopeful class recovered and are well or active after from one to three years.

The carbon dioxide combining power and plasma chlorides obtained before venoclysis failed to indicate the presence of antecedent alkalosis in those cases which responded well, or of antecedent acidosis in those which reacted badly; and any degree of acidosis that may have been induced by the venoclysis was not detectable by these determinations. It is hoped that investigations now in progress may clarify the indications for the use of ammonium chloride by vein.

STUDIES ON THE COLLATERAL CIRCULATION OF HEARTS WITH ACUTE CORONARY OCCLUSION. *Myron Prinzmetal, M.D.; H. C. Bergman, Ph.D.; H. E. Kruger, M.D.; Lois Schwartz, M.D.; Benjamin Simkin, M.D.; and Sidney S. Sobin, M.D., Los Angeles.*

Radioactive red cells were injected intravenously into moribund patients and the distribution of the red cells in the heart was determined after death by means of direct Geiger counts and radioautographs of the heart. In two human hearts with myocardial infarction, the number of red cells was the same in the infarcted and normal areas of the heart.

These unexpected findings prompted a series of acute experiments in dogs. A branch of the left coronary artery was ligated. Radioactive red cells were injected intravenously and later the heart was stopped by freezing. The distribution of red cells was determined. The red cells were distributed throughout the entire heart within one minute after injection. The quantity of circulating blood in the pericardial surface of the ischemic area was equal to that of the surrounding control areas.

In order to determine if collateral blood came from Thebesian vessels or anastomoses from other coronaries, fluorescein was injected intravenously in animals with ligated coronary arteries. The fluorescein was seen to enter the ischemic area from contiguous areas.

It was therefore concluded that the collateral circulation to the ischemic area was derived from anastomotic channels between the coronary arteries.

HEMOLYTIC ANEMIAS, CONGENITAL AND ACQUIRED. *Robert S. Evans, M.D., San Francisco.*

Observations of the longevity of transfused cells in patients with hemolytic anemia have

demonstrated a fundamental difference in the pathogenesis of acquired hemolytic anemia with spherocytosis and congenital hemolytic jaundice. Normal erythrocytes have a reduced survival time in patients with acquired hemolytic anemia, indicating the presence of a hemolysin active against all erythrocytes. On the other hand, transfused cells have a normal survival time in patients with congenital hemolytic jaundice indicating that the accelerated hemolysis in this disease is due to a defect in the patient's erythrocytes.

The presence of an immune body type of hemolysin can be demonstrated on the surface of erythrocytes in acquired hemolytic anemia by the susceptibility of the cells to agglutination in an anti-human globulin rabbit serum. Normal erythrocytes and those from patients with congenital hemolytic jaundice do not agglutinate in the immune serum. The hemolytic antibody found in the acquired form can be eluted from the cells and transferred to normal cells in vitro.

Eight patients with acquired hemolytic anemia have been studied with the above techniques. A hemolysin has been demonstrated in each case, by one or both methods. Studies following splenectomy indicate that response to splenectomy depends on the cessation of production of the immune body. Studies of three patients with congenital hemolytic jaundice have failed to demonstrate the presence of a hemolytic antibody. In one patient a hemolytic crisis followed transfusion but it was evident that only the patient's own cells and not the transfused cells were involved in the rapid hemolysis.

PATHOGENESIS OF INTRASPLENIC OVARIAN TUMORS IN RATS. *Gerson R. Biskind, M.D.* and *Richard Pencharz, Ph.D., San Francisco.*

The transplantation of an ovary into the spleen of a castrate rat places that ovary in a unique hormonal situation. It has been shown previously that the liver is the site of inactivation of the sex hormones. Transplantation of the ovary into the portal circulation permits the hormones it elaborates to pass directly to the liver where they are inactivated. Thus, there is present active ovarian tissue in an animal that exhibits castrate features particularly in the vagina, uterus and hypophysis. The transplanted ovarian tissue responds with excessive growth to gonadotrophic stimulation from the hypophysis. After varying periods up to one year, the transplanted organ becomes transformed

into a tissue which has the histologic appearance of a neoplasm. The most common histologic pattern observed is a lutcoma; in addition, in many of the lutcomas there are nests of proliferating small cells that simulate the pattern of a granulosa cell tumor.

A series of rats have been prepared by operation and then sacrificed at regular intervals to determine the consecutive histologic changes that take place in the transplanted ovary. From these observations, the histogenesis of this tumor will be described and illustrated by lantern slides. Variations in the histologic pattern of the tumor will also be illustrated. Other factors concerned in the pathogenesis of the tumor will be discussed.

PLASMA CELL RESPONSE IN IMMUNIZED ANIMALS. *Thomas F. Dougherty, M.D., Salt Lake City.* (Introduced by *H. H. Lerner, M.D.*)

Since numerous plasma cells are found in tissues of hyper-immunized animals it has been suggested that these cells are concerned with the production of antibodies.

It was noted in this laboratory that the numbers of plasma cells increase in the tissues of animals following successive dosages of antigens. In order to determine whether the occurrence of plasma cells was correlated with the production of antibody, mice of the CBA strain were given a single injection of either sheep red corpuscles or of staphylococcus toxin. Serologic and histologic studies were carried out at intervals of two hours for the first day and daily for six days thereafter. Antibody to either of these antigens appeared on the fourth day and maximal titers were found on the seventh day. Another group of animals received a second dose of the same antigen on the seventh day.

Immediately following the initial immunizing injection a slight increase in numbers of plasma cells occurred but on the seventh day were not more frequent than in the non-immunized animal. Lymphocytes contained antibody on the seventh day. Six hours after the second injection of the same antigen there was a marked increase in numbers of typical Marschalko type plasma cells derived from lymphocytes in the lymphatic tissues.

Although plasma cells may contain antibody they are primarily reaction cells to antigens to which the animal has been sensitized. The Marschalko plasma cell is very probably a

morphologic alteration due to an antigen antibody reaction within or at the surface of a lymphocyte which contains antibody to a specific antigen.

USE OF ALLANTOIN AS A MEASURE OF GLOMERULAR FILTRATION IN THE RAT, DOG AND MAN. *Meyer Friedman, M.D.; Sanford O. Byers, M.D.; and Paul Abrams, M.D., San Francisco.*

Twenty-one allantoin clearances were done on twenty normal rats and compared with the creatinine clearances of seventeen other rats. The respective clearances were 33.7 and 34.6 cc. per 100 Gm. body weight per hour, indicating the essential similarity of the two clearances.

Twenty allantoin and twenty creatinine clearances were performed simultaneously on five normal dogs. It was found that the average allantoin clearance (89.9 cc. per sq. M. per minute) was approximately the same as the average creatinine clearance (89.3 cc.).

Five normal men were given 10 Gm. of allantoin by mouth and two hours later, clearance studies were done. It was found that the average clearance was 124.6 cc. per minute per 1.73 sq. M. This is of the same magnitude as the inulin clearance (125.0 cc. in our previous studies).

In view of the fact that the allantoin clearance was similar to the creatinine clearance in rats and dogs and of the same value as the inulin clearance in man, it is believed that the rate of renal excretion of allantoin may be used to study the rate of glomerular filtration in both the animal and man. The complete absence of toxicity following the oral ingestion of allantoin, its much greater solubility than inulin in urine, the avoidance of intravenous administration and its easier chemical determination—all of these things make the allantoin clearance a more suitable clinical test for estimation of glomerular filtration than the inulin clearance.

RESPIRATION OF HUMAN PLACENTAL TISSUE FROM NORMAL AND ECLAMPTIC PREGNANCIES. *Hal P. James, M.D.; Henry W. Elliott, Ph.D.; and Ernest W. Page, M.D., San Francisco.*

The oxygen consumption of freshly delivered human placental tissue was studied by the direct method of Warburg. The general relationship between placental age and CO₂ established by

Wang and Hellman was confirmed. Endogenous CO₂ values ranges from 7.01 at forty-seven days' conception to a mean of 1.9 at term. In comparison to the normal placenta of corresponding age, placental tissue from women with pre-eclampsia or eclampsia showed a marked decrease in oxygen consumption, an effect not observed in other hypertensive complications of pregnancy. The relationship which this finding bears to the known histologic changes of the eclamptic placenta is discussed.

EFFECTS OF TEMPERATURE AND EXERCISE ON VENOUS PRESSURE IN THE FOOT WHEN IN THE ERECT POSTURE. *James P. Henry, M.D., Los Angeles.*

The venous pressure in the foot in the erect posture was measured by cannulation to a vein in the dorsum. The cannula was attached either to a water manometer or to a pressure sensitive tipped catheter which permitted free movement of the foot. It was found that the pressure is dependent upon the environmental temperature as well as upon the activity of the limb. When the subject is still, the venous pressure attains approximately the full hydrostatic head regardless of the environmental temperature. Standing-walking at an environmental temperature of 65° to 75°F. will lead to a mean venous pressure at or less than knee level. The same exercise when the foot temperature is maintained at 104° to 113°F. will produce a mean venous pressure which supports a blood column extending up to the inguinal level. The mechanism of development of the dependent edema observed in hot weather may be related to these observations. It is suggested that in these conditions blood flow increases due to vasodilation and the rate of pumping of blood and lymph by muscle action does not increase correspondingly. As a result the mean venous pressure may rise significantly above the normal level and edema develop.

EFFECTS OF LOCAL VENOUS CONGESTION ON CARBON MONOXIDE-AVAILABLE VOLUME AND ON MIXING CURVES OF CARBON MONOXIDE AND T-1824 IN VENOUS BLOOD. *Ellen Brown, M.D.; James Hopper, Jr., M.D.; Charles Mudrick, M.D.; and John J. Sampson, M.D.; San Francisco.*

Studies were made using a closed system CO method to determine (a) whether total blood

volume can be measured when in portions of the vascular tree circulation is slowed by local increases of venous pressure, and (b) whether localized congestion affects mixing of CO or T-1824.

CO-available erythrocyte mass was calculated from hematocrit and CO content of blood samples; blood and plasma volumes were accurate only insofar as venous hematocrit approximated body hematocrit. Congestion was produced by inflation of pneumatic cuffs surrounding both thighs and one arm to between 0 and 10 mm. Hg below diastolic blood pressure. Three normal human subjects were used for each of the following experiments:

1. After ten minutes of prior congestion, CO-available volume was determined during congestion and at intervals after release of cuffs. CO-available erythrocyte mass ten to eighteen minutes after release was not significantly greater than during congestion.

2. Venous blood concentrations were measured at thirty and sixty-second; subsequently at longer intervals after introduction of CO and T-1824. Mixing curves were similar whether made at rest or during congestion.

3. To determine volumes of blood accumulated in limb veins during congestion, cuffs were inflated suddenly to 200 mm. Hg after ten minutes of venous congestion. Six to eleven minutes after release of cuffs CO-available blood volume was 1,120 to 1,630 cc. greater than during arterial occlusion.

It is concluded that blood accumulated in vascular reservoirs of the extremities is accessible to CO and T-1824. Venous stasis involving at least a quarter of total blood volume could not be detected by the methods employed.

EXPERIMENTAL LESIONS OF THE PULMONARY ARTERY ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS. *Sanford E. Leeds, M.D., San Francisco.*

Experimental patent ductus arteriosus may be produced in dogs by a side-to-side anastomosis between the aorta and pulmonary artery or by an end-to-end anastomosis between the subclavian or innominate arteries and the pulmonary artery. (*Leeds, Am. J. Physiol.*, 1943.)

In chronic experiments fibrotic intimal plaques may be found on the wall of the pulmonary artery opposite the opening of the ductus. The plaques consist of collagenous and reticulum fibers and a few flattened fibrocytes. Lipid

material is not demonstrated. Possible explanation of the pathogenesis of the plaques and their relation to those described in man in association with patent ductus arteriosus will be discussed. Artificial ductus arteriosus is now produced in children with pulmonic stenosis to relieve the latter condition and lesions on the pulmonary artery may be expected to follow on the basis of the experiments outlined above. Lantern slides will be presented.

EXPERIMENTAL CARDIAC HYPERTROPHY: THE ACUTE EFFECTS OF PULMONARY AND AORTIC STENOSIS. *Arthur Selzer, M.D., and Frank Gerbode, M.D., San Francisco.*

Cardiac hypertrophy in animals has been produced successfully by various methods, mostly reproducing clinical conditions known to be associated with enlargement and hypertrophy of the heart. Little information, however, is available as to the speed with which the heart muscle grows in response to a stimulus.

The purpose of this study was to investigate the degree of hypertrophy developing acutely after experimental aortic or pulmonary stenosis. A method was developed of constricting the first portion of the aorta or pulmonary artery, respectively, by a band of fascia lata with a gradually progressive stenosis over a period of about forty-five minutes. This method led to a considerable reduction in mortality from corrosion of the constricted vessel and from cardiac failure.

Successful stenosis was produced in fourteen dogs, that of the aorta in twelve and the pulmonary artery in two. The animals were sacrificed in two or three weeks. In seven dogs the degree of hypertrophy was measured by the heart-weight-to-body-weight ratio, and the other seven were puppies with identical litter mates used as controls. At autopsy stenosis was found to be mild in five animals and moderate in nine. All animals with moderate stenosis showed definite hypertrophy with a maximum of 65 per cent increase over control animal. Histologic examination revealed marked increase in the size of muscle fibers.

These results were compared with experiments of Herrmann and Holman who used similar methods but extended their experiments for many weeks and months. It is concluded that the degree of cardiac hypertrophy developing within three weeks is comparable to results of experiments extending for long periods of

time. This implies that hypertrophy of the heart is an acute process with most of the growth occurring within a short time after the stimulus for hypertrophy is established.

ARREST OF THERMAL PANTING BY TYPHOID-PARATYPHOID VACCINE ADMINISTRATION.
V. E. Hall, M.D.; F. A. Ellis, M.D.; B. Panzer, M.D.; and R. Grant, M.D., San Francisco.

In fever the activity of the physiologic mechanisms for the dissipation of heat is reduced. In furred animals panting is important among these mechanisms. In a study of fever evoked in rabbits by the intravenous injections of typhoid-paratyphoid vaccine, we have found that thermal panting is arrested about fifteen minutes after vaccine administration. Panting can be restored, however, by increasing the body temperature to a new high level. Thus the body temperature threshold for panting is elevated by the vaccine. Since the respiratory response to inhalation of 5 per cent CO_2 -95 per cent O_2 is not impaired by vaccine administration, it is improbable that the vaccine depresses the medullary respiratory center. Whether panting is arrested by depression of the pontine pneumotaxic center or a higher respiratory mechanism is now under investigation.

PERTUSSIS AGGLUTINOGEN SKIN TEST. *John J. Miller, Jr., M.D.; Mary L. Ryan, M.D.; and Edward Havard, M.D.; San Francisco.*

One hundred children who had received H. pertussis vaccine in variable dosage two months to eight years previously were skin tested with the acid extracted H. pertussis agglutinin of Felton, Smolens and Mudd. Determinations of their serum agglutinins for H. pertussis were performed concurrently with a technic which has been correlated with clinical immunity. A significant association was found between "positive-immune" skin reactions and high agglutinin titers consonant with clinical immunity. On the other hand there was no significant association between "negative-susceptible" skin reactions and low serum antibody. Ten per cent of the children had "negative-susceptible" skin reactions while carrying high titers of agglutinins.

In children who had received vaccine more than a year previously a positive correlation between the total dose of vaccine and the degree of skin reactivity was observed.

In children who had received a total dose

of more than 80 billion (saline suspended) H. pertussis, it was found that skin hypersensitivity did not decrease with time until four years after the administration of vaccine. Serum agglutinin levels roughly paralleled the skin reactions.

The skin tests stimulated an increase in serum antibody in 68 per cent of fifty children whose sera were titrated a week thereafter. Intradermal injections also increased the reactivity of the skin itself. Agglutinin is therefore antigenic.

Ten children with unquestionable histories of pertussis during the past twelve years were skin tested. In only one was a "positive-immune" reaction elicited.

CONCLUSION

Skin hypersensitivity to acid extracted H. pertussis agglutinin is a valid index of immunity in children who have received H. pertussis vaccine in the past. A lack of hypersensitivity, however, is not necessarily an index of susceptibility. In children who have recovered from an attack of pertussis, testing with agglutinin is misleading (and unnecessary) as many individuals may exhibit no hypersensitivity.

EFFECT OF BENZOIC ACID ON PENICILLIN BLOOD LEVELS AND RENAL FUNCTION.

John F. Waldo, M.D. and Wan Ching Lu, M.S. Salt Lake City. (Introduced by M. M. Wintrobe, M.D.)

Daily penicillin levels were measured in early luetics receiving rapid treatment without arsenicals. During a four-day control period daily penicillin levels and blood urea nitrogens as well as the initial endogenous creatinine clearance were determined. Following this the patients were given 12 Gm. of benzoic acid per day for five days, an amount about as great as could be tolerated. During this time penicillin levels and blood urea nitrogens were determined daily. Creatinine clearance was repeated at the end of the period and when possible on the second day of benzoic acid administration.

There was no consistent alteration in the blood penicillin levels associated with the administration of benzoic acid. In a few cases the blood urea nitrogen rose temporarily but usually it returned to normal even though the benzoic acid was continued. The creatinine clearance showed no significant variation at any time. It is concluded that benzoic acid, given in the stated amount, is ineffective in raising the blood

level of the penicillin. There appears to be no permanent damage to the kidney by the use of this drug.

USE OF INFLUENZA VIRUS VACCINE IN CHILDREN. *Henry B. Bruyn, M.D.; Gordon Meiklejohn, M.D.; and Henry D. Brainferd, M.D., San Francisco.*

The extensive use of the combined Type A and Type B Influenza Virus Vaccine in adults has established the dosage and expected serologic response. This information is at present not available for its use in children, save for arbitrary dose schedules and one report giving such a high incidence of reactions as to contraindicate its use.

The intradermal route of inoculation has been used for this vaccine in adults with satisfactory serologic response and rare reaction.

The present investigation concerns the inoculation of seventy-nine children, aged one year to fourteen years, using this vaccine subcutaneously and intradermally in a variety of doses, and measuring the serologic response.

The incidence of febrile reaction to subcutaneous vaccine was 59 per cent, almost all involving temperatures over 101°F. and obvious symptoms. Following 0.1 cc. intradermally, the incidence was 26 per cent and was 36 per cent after 0.1 cc. twice, separated by three days rarely with temperatures over 101°F. and never with overt symptoms.

The fold increase in antibody to Type A and Type B Influenza following 0.5 cc., 0.25 cc. and 0.125 cc. subcutaneously and 0.1 cc. intradermally was equal or better than the results reported for adults. The response to 0.1 cc. intradermally given twice was most consistent and over twice the adult response.

The average post-vaccination titre to the two types was as high or higher than in adults, following 0.5 cc. and 0.25 cc. subcutaneously and 0.1 cc. twice intradermally.

Averaging all routes and doses, children under seven years of age had less increase and lower final titres than those over seven.

The higher pre-vaccination titres yielded smaller increases in antibody.

CLINICAL VALUE OF UNIPOLAR EXTREMITY LEADS. *Maurice Sokolow, M.D., San Francisco.*

The practical clinical value of multiple precordial leads has been clearly established. Not

so well appreciated has been the practical aid obtained from unipolar extremity leads. A study was made in 1,000 patients of the unipolar leads with particular emphasis on their value in providing information not obtained from the standard limb and unipolar precordial leads. The findings are summarized as follows:

1. The presence of a significant Q wave in lead aV_L may be the only clue to lateral myocardial infarction and indicate the advisability of high precordial leads in addition to the usual positions. The standard limb and six precordial leads may be normal or, if abnormal, of no characteristic pattern. Wilson, as well as Myers, has also called attention to the value of lead aV_L in the diagnosis of lateral myocardial infarction.

2. A study of the Q wave in lead aV_F is often decisive in the interpretation of Q wave in standard lead III. In posterior myocardial infarction, the Q wave reflecting potential changes from the basal surface of the heart is transmitted to the left leg and it is only when the Q wave in III is due to a significant Q wave in aV_F that the Q₃ is diagnostic.

3. ST-T changes in aV_L (horizontal hearts) or aV_F (vertical hearts) may be the first sign of left ventricular hypertrophy and may precede the ST-T abnormalities in V₅, V₆ or the standard limb leads.

4. Abnormalities in lead aV_L typical of left ventricular hypertrophy or left bundle branch block may occur with normal appearing V₅ and V₆ if (a) the electrodes were placed too far to the right or (b) the transitional zone is displaced to the left.

5. In progressive left ventricular hypertrophy, ST-T abnormalities first appear in aV_L or aV_F and later in aV_R. The presence of an abnormal upright T in aV_R is helpful evidence of a more advanced degree of hypertrophy.

6. Questionably abnormal right and left axis deviation may be shown by unipolar limb leads to be due to marked vertical or horizontal position of the heart, and in association with the precordial leads may differentiate normal from abnormal axis deviation.

7. Unusual rotation of the heart may at times be clarified by a study of the unipolar limb leads.

8. The electrocardiographic position of the heart, as obtained by unipolar limb leads, may clarify atypical abnormalities in the standard leads such as: (a) ST-T changes in lead II and III without axis deviation in left ventricular

hypertrophy in vertical hearts; and (b) Q waves in lead I instead of II and III in posterior myocardial infarction in horizontal hearts.

OBSERVATIONS ON THE HUMAN HEART DURING INDUCED HYPOXIA (THE ISCHEMIA-INJURY PATTERN). *Hans H. Hecht, M.D.; Junior A. Abildskov, M.D.; Robert C. Bolin, M.D., and Ferne S. Focht, M.D., Salt Lake City.*

One hundred thirty-five patients were subjected to inhalation of a gas mixture consisting of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or less. Thirty-six tests were performed on presumably normal individuals, fifty-five on patients with signs and symptoms of coronary insufficiency and forty-four on patients who had suffered one or more episodes of proven myocardial infarction. No adverse reactions were encountered. A sudden fall in arterial pressure occurred in eight patients and necessitated interrupting the test.

In this report only the electrocardiographic changes observed are to be discussed. Levy's standardized technic was replaced by a more flexible system which included a number of semidirect unipolar leads, unipolar and bipolar limb leads. This modification permitted a detailed analysis of site, size and penetration of the anoxic regions not possible by Levy's method. Phases of ischemia and phases of injury similar to those demonstrable in animal experiments (Bayley) were readily recognized. Subendocardial involvement was contrasted with epicardial lesions. All changes observed were quickly reversible.

The following conclusions appear justified: (1) The phase which can be induced during hypoxia indicates the severity of the underlying pathologic process. (2) Coronary insufficiency may be confined to certain myocardial regions and may leave other sections uninvolved. By the use of the technic proposed, the location, depth and extension of the abnormal zone can be demonstrated. (3) In patients who have suffered from myocardial infarction failure to alter the resting pattern suggests that adequate collateral circulation has been established. (4) Reversal of the electrocardiogram taken over the infarcted region from the ischemic to the injury pattern signals inadequate collateral circulation. (5) Ischemic areas may appear during the test at sites remote from a previously infarcted region. They may be responsible for

residual anginal pain following occlusion of one coronary artery.

The method as outlined permits a rational interpretation of coronary artery disease. The test has prognostic value.

TREATMENT OF GRAVES' DISEASE WITH RADIOIODINE. *Earl H. Miller, M.D. and Mayo H. Soley, M.D., San Francisco.*

Iodine¹³¹ (half life of eight days) has been administered to fifty-six patients with Graves' disease. Thirty-six of these patients have been followed sufficiently long to warrant evaluation of this method of therapy.

Three patients have been followed since October 12, 1941. Two have been normal for over five years; the third is normal except for questionable mild hypothyroidism. Of three other patients treated late in 1941 and early in 1942, two could not be followed and the third died of cerebral embolism during an attack of auricular fibrillation.

Thirty-three patients have been treated since July, 1945, and have been studied for a minimum period of six months and maximum of twenty-seven months. Of these, twenty-five patients have been classified as satisfactory in terms of their response. The average basal metabolic rate, protein-bound iodine, size of thyroids, time to return to normal and dose of Iodine¹³¹, are as follows:

	Before Treatment	After Treatment
BMR.....	+28%	-10%
PBI.....	10.7 microgram %	5.7 microgram %
Thyroid.....	31 Gm.	13 Gm.

Time to return to normal: 3.6 months
Dose of I¹³¹: 2,726 microcuries

Eight patients were classified as unsatisfactory either because they took too long to return to normal or have not yet returned to normal.

	Before Treatment	After Treatment
BMR.....	+43%	+10%
PBI.....	12.9 microgram %	6.9 microgram %

	Before Treatment	After Treatment
Thyroid.....	43 Gm.	22 Gm.

Dose of I¹³¹: 5,537 microcuries

CHRONOLOGIC SEPARATION OF WATER AND CHLORIDE DIURESIS IN NEPHROTIC SYNDROME. *David A. Ryland, M.D., San Francisco.*

In a girl, aged four years, the nephrotic syndrome (pure lipoid nephrosis?) began abruptly during a serum sickness-like reaction to beesting. Early in the course of the syndrome, events moved quickly; it was then possible to examine individually some eighty-five consecutively voided specimens of urine (only a few were lost) through three spontaneous cycles of exacerbation and remission within a short time. Determinations included specific gravity, pH, and rates of excretion of water, chlorides, protein and formed elements.

In general, a rise of urinary pH was the earliest indication of approaching remission. This was soon followed by water diuresis. Finally the rate of chloride excretion increased, sometimes more than twenty-four hours after urine flow had become elevated. The time at which proteinuria decreased was variable within this sequence, and the numbers of formed elements were even more capricious.

Other workers have similarly shown chronological differences in behavior of water and of electrolytes (a) as edema collects during drug fever and (b) during the action of diuretics in patients with congestive heart failure.

The present findings suggest separate abnormalities in the renal excretion of water and of chlorides in the nephrotic syndrome.

EFFECTS OF LIPOTROPHIC AGENTS ON THE PROTEIN BALANCE IN PATIENTS WITH LIVER DAMAGE. *Laurence W. Kinsell, M.D.; George D. Michaels, M.D.; Harry A. Weiss, M.D. and Harry C. Barton, M.D., Oakland.*

In view of the role of choline and methionine in the prevention and treatment of liver damage in experimental animals, it was decided to attempt to evaluate the effects of these agents upon patients with liver disease. One such investigative effort was that of the determination of the effects of these agents upon the protein balance in such individuals.

The data here presented indicate that both methionine and choline will, in certain circumstances produce a strongly positive nitrogen balance. The theoretic considerations involved in these findings are discussed.

PSYCHODYNAMIC AND HYPOTHALAMO-HYPOPHYSIAL ASPECTS OF FERTILITY. *Harry B. Friedgood, M.D., Los Angeles.*

Correlation of the available anatomic, physiologic and clinical data discloses that the nervous system influences the functional activity of the adeno-hypophysis, probably through neuro-humoral means. The hypothalamo-hypophyseal area plays an important role in the pathogenesis of impotence and in the mechanism by means of which emotional conflicts disturb gonadal function.

STUDIES ON ACTIVE IMMUNITY AGAINST TETANUS. *John J. Miller, Jr., M.D. and Mary L. Ryan, M.D., San Francisco.*

Tetanus antitoxin titrations in children following basic immunization with fluid alum precipitated and aluminum hydroxide adsorbed tetanus toxoid were compared. Over a period of four years the last mentioned was found to produce and maintain higher levels of antitoxin.

The speed of increase in circulating antitoxin in previously immunized individuals following reinjection with fluid, alum precipitated, and aluminum hydroxide adsorbed tetanus toxoid was compared. Fluid toxoid was found to be most rapidly effective.

The laboratory and field evidence (from the British Army) for and against the use of tetanus antitoxin in actively immunized individuals is briefly reviewed.

The application of this information to the treatment of contaminated wounds in ex-service men (and tetanus immunized children) is discussed. It is concluded that (1) routine biennial reinjections with adsorbed toxoid be encouraged in ex-service men, (2) fluid toxoid is the agent of choice as a wound booster, (3) prophylactic antitoxin is not contraindicated and occasionally may be advisable as in cases of compound fractures or gunshot wounds.

COMPARATIVE STUDY OF THE EFFECTS OF ADMINISTRATION OF LARGE DOSES OF HORSE SERUM AND HUMAN ALBUMIN TO RABBITS WITH REFERENCE TO FORMED ELEMENTS OF THE BLOOD, PLASMA PROTEIN CONSTITUENTS AND IMMUNOLOGIC CHANGES. *B. V. Jager, M.D. and R. J. Nelson, M.D., Salt Lake City.*

The clinical and experimental observations that serum sickness may result in pathologic

lesions simulating those of periarteritis nodosa and acute rheumatic fever suggest that a study of certain hematologic and immunologic aspects of experimental serum sickness in animals might offer useful information.

One group of ten rabbits was given intravenously, a single large dose of horse serum (mixed antigen); a similar group received a single large dose of human albumin (relatively homogeneous antigen); while a third group of equal number served as controls. Specimens of blood for various studies were obtained repeatedly from each group during a seven-week period following injection of foreign protein.

With the exception of a transient lymphopenia which followed injection of albumin or horse serum, the injection of foreign proteins did not lead to significant changes in the packed red cell volume, total and differential leukocyte counts and the reticulocyte response when contrasted to the control group.

In spite of inherent difficulties attributable to animal variation, the rabbits receiving horse serum showed a moderate increase in plasma fibrinogen and a delayed rise in total globulin and "gamma globulin" (determined chemically). No significant reduction in serum albumin occurred. By contrast no impressive changes occurred in these protein constituents in the animals receiving human albumin.

After injection of antigen, circulating precipitinogen persisted much longer and precipitins appeared earlier in the group receiving horse serum than in the one receiving human albumin. Antibodies to a globulin fraction of horse serum seemed to develop earlier than antibodies to horse serum albumin.

The total quantitative serum hemolytic complement decreased following administration of

horse serum but not after injection of human albumin.

COMPARISON OF CHEMICAL DETERMINATIONS OF SERUM ALBUMIN CONCENTRATION WITH CORRESPONDING ELECTROPHORETIC PATTERNS. *T. B. Schwartz, M.D., Salt Lake City.* (Introduced by B. V. Jager, M.D.)

Numerous observers have shown that the commonly used sodium sulfate precipitation methods of Howe for the determination of serum albumin concentration gives falsely high values when compared to those obtained by electrophoresis. In view of the obvious need for a simple, easily executed reasonably reliable clinical procedure for estimating albumin concentration in normal and pathologic sera, the results obtained by three precipitation techniques were compared with values obtained by electrophoresis. All four procedures were carried out on aliquots of individual samples of both normal and abnormal sera, the albumin concentration ranging from 17 to 64 per cent in the series of sera tested.

As noted by others, the Howe method (21.5 per cent sodium sulfate) yielded serum albumin concentrations that were 4 to 20 per cent higher than those determined electrophoretically.

The methanol precipitation procedure described by Pillemer was found to be technically difficult to control and, in pathologic sera, gave results which were consistently lower than the electrophoretic values.

Precipitation of serum globulins by saturated magnesium sulfate (Popjak and McCarthy) was found to be a reliable and relatively accurate method for serum protein partition, yielding serum albumin values which correlated closely with those obtained by electrophoresis.

Book Review

Medicine in the Changing Order. Report of the New York Academy of Medicine Committee on Medicine and The Changing Order. Pp. 232. New York, 1947. The Commonwealth Fund. Price \$2.00.

"Medicine in the Changing Order" is a carefully prepared, comprehensive report of the results of a well planned study by a committee whose objective was "to be informed on the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and in its services to the public may be preserved and embodied in whatever new social order may ultimately develop." The composition of the committee is of interest in that it is representative of various lay groups, such as insurance companies, social welfare, labor, industry, the ministry and law, physicians interested in medical education and public health and dentistry and nursing.

The report begins with a chapter briefly reviewing the history of American medicine. It passes on to medicine in the last decades and an estimate of the health of the nation

at the present time, emphasizing wide regional differences. The succeeding chapters, covering medical care, preventive medicine, the hospital, nursing and medical insurance, contain calculated estimates of the faults and benefits of the existing institutions, or the lack of them, with specific suggestions in each instance as to how remedies and improvements may be effected. For ready reference there is a summary at the end of most chapters listing the proposed changes. The final chapter entitled "The Method and The Goal" is a summary of the ideals and conditions which are attendant upon good medical care.

The conclusions of the Committee are admirable. They are of particular interest in this time of increasing socialization. Socialized medicine is rejected in favor of voluntary pre-payment plans plus government aid. The importance of the cooperation of physicians is realized and the inefficiency of bureaucratic administration is deprecated. This critical study is, in the opinion of this reader, not only of general interest but should be required reading for politicians and members of the medical profession.

B. H.

Editorial

Penicillin and Glutamic Acid

MORE than eight years have passed since penicillin was first used in the treatment of bacterial infections. The chemical structures of several penicillin species have recently been determined, and the drug has even been synthesized in the laboratory. As yet, however, its mode of action is unknown.

Most gram-negative bacteria are able to synthesize the majority, if not all, of the amino acids needed in their cellular metabolism. Many gram-positive organisms, on the other hand, have more exacting nutritional requirements and are unable to synthesize many of the chemical units necessary for protein formation and other metabolic functions. Moreover, the metabolic processes of gram-positive organisms are more susceptible to interference by bacteriostatic agents than are those of most gram-negative bacteria. Recently, E. F. Gale and his collaborators¹⁻⁶ have under-

taken a systematic study of the metabolism of certain amino acids by both gram-positive and gram-negative bacteria and have investigated the effect of several classes of antimicrobial agents including penicillin upon these important metabolic processes. Utilizing specific decarboxylating enzymes to measure the concentration of selected amino acids within bacterial cells, they have made the following observations relating to the mode of action of penicillin:

1. Gram-positive organisms in general are able to assimilate glutamic acid and lysine from the external medium and to concentrate them within the internal environment whereas gram-negative organisms are unable to do so.

2. Although lysine appears to enter gram-positive cells by diffusion, glutamic acid cannot pass across the cell wall unless energy is supplied by some exergonic metabolism, such as the fermentation of glucose.

3. Once glutamic acid has entered gram-positive micro-organisms, it is present in a free state and serves as a source of amino acid for protein synthesis and other metabolic functions in growing cells.

4. When gram-positive bacteria are grown in penicillin, the assimilatory mechanism for glutamic acid is blocked; and since internal metabolic processes are not affected by the drug, the level of free glutamic acid within the cell decreases to a point where growth can no longer occur.

¹ GALE, E. F. The bacterial amino-acid decarboxylases. *Adv. in Enzymol.*, 6: 1-32, 1946.

² GALE, E. F. The assimilation of amino-acids by bacteria. 1. The passage of certain amino-acids across the cell wall and their concentration in the internal environment of *Streptococcus faecalis*. *J. Gen. Microbiol.*, 1: 53, 1947.

³ TAYLOR, E. S., The assimilation of amino-acids by bacteria. 3. Concentration of free amino-acids in the internal environment of various bacteria and yeasts. *J. Gen. Microbiol.*, 1: 86, 1947.

⁴ GALE, E. F. and TAYLOR, E. S. The assimilation of amino-acids by bacteria. 5. The action of penicillin in preventing the assimilation of glutamic acid by *Staphylococcus aureus*. *J. Gen. Microbiol.*, 1: 314, 1947.

⁵ GALE, E. F. Correlation between penicillin resistance and assimilation affinity in *Staphylococcus aureus*. *Nature*, 160: 407, 1947.

⁶ GALE, E. F. and RODWELL, A. W. Amino-acid

metabolism of penicillin-resistant staphylococci. *J. Bact.*, 55: 161, 1948.

5. The concentrations of penicillin needed to prevent assimilation of glutamic acid by various gram-positive organisms are of the same order as those needed to prevent their growth.

6. Penicillin-resistant mutants assimilate glutamic acid less efficiently than the sensitive parent strain, there being a quantitative relation between the assimilation affinity and penicillin sensitivity of the organism.

7. *Staphylococcus aureus* when rendered resistant to high levels of penicillin not only loses its ability to assimilate glutamic acid

but also becomes gram-negative and, like other gram-negative organisms, is able to synthesize all of its amino acid requirements from ammonia and glucose in the presence of thiamine.

The above observations from Gale's laboratory strongly suggest that the mode of action of penicillin involves a disturbance in the uptake of amino acids by susceptible bacterial cells. The exact manner in which the penicillin interferes with the assimilation of amino acids is at present unknown.

W. BARRY WOOD, JR., M.D.

Symposium on Aviation Medicine

Physiologic Problems in Aviation

HERMAN S. WIGODSKY, M.D.* and JAN H. TILLISCH, M.D.†

Washington, D. C.

Rochester, Minnesota

THERE are certain physiologic problems that are unique to aviation. Among these problems are those which arise as a result of low barometric pressure—anoxia and decompression sickness. Other problems are those due to cold and to movement—airsickness, acceleration and deceleration.

The physiologist in aviation, through investigation of these problems, is able to provide the physician with a better understanding of the physiologic mechanisms involved, in this way establishing a more rational basis for the diagnosis and treatment of injuries and diseases found in flying personnel. Furthermore, he provides airmen with information concerning the physiologic hazards which face them, permitting them to meet these hazards intelligently. In addition the physiologist also provides engineers with physiologic data necessary for the proper construction of equipment required to neutralize these hazards.

The following is a discussion of some of the more important physiologic problems in aviation:

ANOXIA

The anoxia encountered in aviation does not differ qualitatively from that experienced by mountain climbers. It results from the lowered partial pressure of oxygen in the inspired air. This in turn results from the lowered barometric pressure. Thus at approximately 18,000 feet (5.5 kilometers) the barometric pressure is only one-half of that present at sea level and the partial

pressure of oxygen is reduced from the sea level normal value of approximately 160 mm. of mercury to 80 mm. of mercury. At this altitude the hemoglobin of arterial blood is approximately 70 per cent saturated with oxygen in contrast to the normal of 97 per cent. Since the earliest balloon flights of Tissandier, the signs and symptoms of anoxia have been encountered and described. The serious symptoms of acute anoxia encountered in ascent vary somewhat in different individuals. In general, however, as high as 14,000 or 15,000 feet (4.3 or 4.6 kilometers) if exposure is not too prolonged there are few symptoms of anoxia because the compensatory mechanisms provide adequate defense for the body. Above 15,000 feet (4.6 kilometers) the compensatory mechanisms no longer suffice and symptoms of anoxia develop. The most striking of these symptoms are retardation of mental and physical processes, impairment of the special senses, especially vision, pronounced fatigue and frequently changes in personality such as euphoria. From 20,000 to 23,000 feet (6.1 to 7.0 kilometers) unconsciousness usually occurs. The unconsciousness may be the result of failure of either the circulatory or the central nervous system. The after-effects of anoxia are headache, lethargy, nausea and vomiting or severe prostration. Recovery usually takes place in twenty-four to forty-eight hours. In modern aircraft anoxia at high altitudes is prevented by the use of oxygen or pressurization of the air.

* Former Director of Research, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

† Former Chief of Medicine, Army Air Force School of Aviation Medicine, Randolph Field, Texas. At present Consulting Physician, Division of Medicine, Mayo Clinic, Rochester, Minnesota.

craft cabin. A number of deaths have been encountered in military aviation either from improper use of oxygen equipment or in a few cases from failure of the equipment.

EXPANSION OF GASES

The mechanical effects of low barometric pressure encountered at high altitudes result from changes in the volume of gases within the body cavities. Boyle's law states that a given quantity of gas varies in volume inversely in proportion to the absolute pressure exerted on it. The structures most commonly affected by the expansion of gases at high altitudes are the middle ear, the paranasal sinuses and the gastrointestinal tract. Of these the ear is most commonly affected. As the barometric pressure is reduced during ascent, the expanding air in the middle ear causes a pressure sensation and eventually becomes sufficiently great to force the air out through the eustachian tube. The pressure within the middle ear then becomes equalized with the outside pressure. During descent in an aircraft the barometric pressure increases and the pressure in the middle ear falls below that of the external air. With this negative pressure in the middle ear it is difficult, or may be impossible, to open up the eustachian tube. Aero-otitis media is the term used to describe the traumatic inflammation caused by the difference of pressure between the external air and the air in the middle ear.

A phenomenon similar to that which occurs in the middle ear takes place in the paranasal sinuses with changes in barometric pressure. If the sinuses are normal, air passes into and out of the cavities and thus produces equalization of pressure at the usual rates of ascent and descent. If the sinusal openings are obstructed for any reason, as in sinusitis, such equalization of pressure does not take place. The difference of pressure between the air in the sinuses and the external atmosphere produces pronounced pain which may occur either on ascent or on descent.

The gastrointestinal tract normally contains gas which varies in amount. The

sources of gas in either normal or abnormal amounts are swallowed air, digestion, fermentation and bacterial decomposition of food, faulty absorption of gas from the gastrointestinal tract and secretion of gas from the blood. Most of the gas is contained in the stomach and the large intestine. During ascent the gases in the gastrointestinal tract expand. Ordinarily, relief is obtained by belching and the passing of flatus. In some persons, however, expansion of gas causes extreme discomfort because of inadequate elimination, pocketing with entrapment of gas in the gastrointestinal tract or excessive gas due to a diet high in gas-forming foods.

DECOMPRESSION SICKNESS

Exposure to low atmospheric pressure such as is encountered at high altitudes may cause another phenomenon in the body, that is, the formation of bubbles in the tissues, blood and other body fluids. This rarely occurs below 25,000 feet (7.6 kilometers). The mechanism is similar to the evolution of bubbles in charged water when the cap of the bottle is removed. The body fluids contain gases, chiefly nitrogen. When the atmospheric pressure is reduced, as in high altitudes, the body fluids become supersaturated with nitrogen and bubbles of gas are formed. The process of production of bubbles, which produces a condition known as "aero-embolism," is the same as the process in caisson disease. It may affect the individual in various ways. The condition known as "bends" is the most common manifestation. The symptoms are pains in the joints, bones or muscles of the extremities. The pain is deep and poorly localized and produces a constitutional reaction out of proportion to its severity. It is aggravated or precipitated by exercise of the affected part. There may be pallor, sweating, faintness, nausea, vomiting or even unconsciousness.

The condition known as "chokes" represents another symptom complex. There is burning substernal distress which frequently is associated with a non-productive cough.

The burning and cough are aggravated by deep breathing and, as a result, the depth of breathing is restricted. The onset of chokes is usually rapid and the symptoms are almost always progressive. The symptoms are ameliorated by descent but residual symptoms may persist after the person has returned to the ground. The exact cause of chokes is not known at the present time but the most widely accepted hypothesis is that the condition is due to pulmonary aero-embolism.

Cutaneous disturbances due to aero-embolism may occur. These disturbances consist in paresthesias and cutaneous rashes. The latter may appear as simple erythema, subcutaneous swelling or ecchymotic discoloration. Defects in the visual fields are encountered infrequently as a result of aero-embolism. Such defects usually are followed by a migrainic-like headache. Both the cutaneous and visual disturbances are probably due to embolic phenomena.

Circulatory reactions due to aero-embolism are the most serious complications. These may be divided into two categories: The first is a syncopal reaction, recovery from which is usually prompt during and following descent to ground level. The second type is rare and is much more serious. It is manifested by symptoms of secondary shock at altitude or after descent to ground level following high altitude flight. The type which develops after reaching ground level may be delayed many hours in its onset. The neurologic symptoms which fairly frequently accompany this type of reaction are usually transitory and vary from hemiplegias to paresthesias. The treatment is identical with that of secondary shock resulting from any other cause; however, these patients must be watched carefully for the development of pulmonary edema.

It is appropriate to mention in this section the problem of "explosive decompression"—a term applied to the sudden lowering of pressure within a pressure cabin airplane. Such an event may result from damage to the cabin by enemy action, from

failure of the pressurizing machinery to function adequately or from failure of a part of the cabin structure itself. This problem is linked intimately with that of decompression sickness and has assumed a place of major importance with the advent and general utilization of pressure cabin aircraft. The problem of explosive decompression is divided into two parts: (1) the immediate effects due to rapid change of pressure *per se* and (2) the effects due to altitude—*anoxia*, decompression sickness and cold. The latter effects differ in no way from exposure to high altitude under other circumstances except for the rapidity with which the person is exposed. The immediate effect, on the other hand, poses new problems in regard to the possible injury to gas-containing organs as a result of high pressure differentials developed during rapid decompression. The lungs are particularly important in this regard.

COLD

The problem of cold in aviation differs only slightly from the same problem in any cold environment. However, in contrast with the latter the aviator is relatively restricted in his movements; he encounters cold suddenly (frequently going from tropical conditions to extremely low temperatures in a few minutes) and the cold is frequently accompanied by violent wind blast. The temperatures encountered may be below -60°C . The problem is complicated by the fact that exposure to cold is intermittent and of relatively short duration thus precluding any great degree of adaptation or acclimatization. Exposure to these extremely low temperatures results in frostbite. There has been renewed interest in this physiologic problem in an attempt to establish more reasonable methods of treatment based on the physiologic changes which occur.

ACCELERATION

The problem of acceleration in aviation has increased in direct proportion to the increased speed of aircraft and the im-

provements in structural design enabling aircraft to withstand larger stresses. World War II intensified both the study of the effect of acceleration on the individual and the development of measures and equipment to combat these effects. These studies have been parallel in their growth and have led to a logical development of protective equipment. Until jet and rocket propelled aircraft were employed, acceleration was principally a problem which resulted from aircraft maneuvers such as spins, turns and pull-ups. However, these newer developments pose serious acceleration problems because of very high speed take-offs and variation in take-off altitudes.

DECELERATION

Large decelerative forces are encountered frequently in aviation and are a formidable

cause of death. Such forces are met with in crash landings, ditchings, high speed bail-outs and bail-outs at high altitudes when the airman opens his parachute immediately after leaving his airplane. Not only is the problem of deceleration of importance to the engineer, who must construct equipment so that the ability of the human body to withstand these forces will not be exceeded, but it is also of importance to the surgeon who must diagnose and treat the injuries which result from these forces. Diagnosis and treatment will be facilitated if the mechanism of the injury is understood.

Studies to ascertain the limits of tolerance of the human body have been undertaken, using animal and human subjects. It has been possible to reproduce in animals the lesions which occur in human beings subjected to decelerative forces.

Medicine in Aviation

JAN H. TILLISCH, M.D.* and FREDERICK R. GUILFORD, M.D.†

Rochester, Minnesota

Galveston, Texas

MEDICINE in aviation may be applied to two groups: the air crew and the passenger. Factors which may be of great importance in air crew members may have no significance in passengers. As has been mentioned in a previous article, on ascending to altitude certain physical changes which affect the body physiology occur, namely, lowered barometric pressure with resultant decreased oxygen tension and expansion of body gases, changes due to motion, such as acceleration and deceleration, and cold. A further change is the individual emotional response to transportation by air. Because of these changes, it is important to consider carefully two groups of aviation subjects, namely, the air crew and the ill patient to be transported by air. The matter of transportation of the ill patient has been emphasized by Grant,¹ Hippke² and Tillisch and his co-workers.³ The indications and contraindications for the aerial transportation of ill patients are not necessarily applicable to the casual air passenger.

The determination of the status of the cardiovascular system is of importance for both pilot and passenger. A hypersensitive carotid reflex has been shown by Tillisch and Lovelace⁴ to be of great importance in the pilot for the reason that it may cause sudden unconsciousness. Therefore a pilot with this condition should be disqualified. The presence of postural hypotension in a pilot is disqualifying for a similar reason as pointed out by MacFarland and his co-workers.⁵ At present the most commonly accepted method of examining for postural hypotension is to have the examinee rest in

a supine position until a basal blood pressure and pulse rate are obtained. The examinee then stands erect for three minutes and the blood pressure and pulse rate are again taken. If a significant fall in blood pressure and rise in pulse rate occur or if the examinee evinces any signs of unconsciousness, a diagnosis of postural hypotension is made. Evidence of signs of unconsciousness is of more importance than the finding of a fall in blood pressure alone. In the examination for postural hypotension it is also helpful to elicit any history of unconsciousness occurring on rising from a supine position. In passengers neither a hypersensitive carotid sinus reflex nor a postural hypotension contraindicates flying.

Valvular heart disease or hypertension has always been considered a contraindication for flying a plane. This question has not been finally settled. Although there has never been a satisfactory statistical analysis to determine the incidence of sudden unconsciousness in patients who have valvular heart disease or hypertension, it is suspected that it would be very little higher in these patients than in a control group. Yet the chief reason for considering these two conditions contraindications for piloting a plane is the supposed increased likelihood of sudden unconsciousness or weakness. A person with severe hypertension or severe valvular heart disease should not fly a plane. In addition a person with cardiac decompensation caused by either of these two conditions or by any other condition had best fly as a passenger only when absolutely necessary and when there is adequate oxygen available. A person with cardiac decompensa-

* Former Chief of Medicine, Army Air Force School of Aviation Medicine, Randolph Field, Texas. At present Consulting Physician in Division of Medicine, Mayo Clinic, Rochester, Minnesota.

† Former Chief of Air Evacuation, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

tion already has anoxia and the added load of the anoxia of altitude on an already impaired circulatory system may have harmful effects. The nervous tension associated with flying may further aggravate the cardiac condition. In the final analysis a person with mild uncomplicated hypertension or well compensated valvular heart disease can probably pilot a plane with safety. One who has moderately severe hypertension or valvular heart disease with even minimal cardiac decompensation had best not fly a plane. The passenger with either hypertension or valvular heart disease can be transported safely by plane unless he has severe hypertension with a history of the complications of hypertension or unless he has frankly decompensated valvular heart disease; in these latter events the passenger had best not fly. If it is necessary for these patients to fly, oxygen should be administered to them from the ground up.

The rôle of coronary heart disease in aviation has been emphasized by Benson,⁶ Graybiel and McFarland⁷ and White.⁸ This condition is of a more serious nature in the pilot than the aforementioned types of heart disease because of the suddenness and severity of the attacks. Evidence of coronary disease in a pilot should contraindicate flying by that person. Coronary heart disease in the passenger must be handled as an individual problem. It is best not to fly for a considerable period of time after myocardial infarction. A person with easily induced anginal attacks had best not fly. The patient who may have marked apprehension to flying which aggravates his coronary disease had best not fly. A trip by plane that necessitates going to higher than normal altitudes should be contraindicated for a person with coronary disease. Generally the patient who has severe coronary disease should be advised not to fly unless other forms of transportation would put even a greater strain on the heart; if he does fly, oxygen should be administered at any altitude above 7,000 feet and a mild sedative prescribed to allay any nervous tension.

Diseases of the respiratory system vary in their rôle as contraindications to flying. The common cold, sore throat and sinusitis all may increase susceptibility to aero-otitis and aerosinusitis. The application of the usual vasoconstrictor drugs, such as amphetamine (benzedrine) or 2-aminoheptane sulfate (tuamine), may shrink the tissues in the nasopharynx and nasal cavity so that the middle ear or accessory sinuses can be adequately ventilated. Bronchitis, bronchiectasis, pneumoconiosis, pulmonary abscess and bronchogenic carcinoma are not in themselves contraindications to the patient's flying as a passenger unless such conditions are sufficiently severe as to cause respiratory embarrassment. In the latter event these persons should not fly unless oxygen is available and is used. Patients suffering from pneumonia also should be given oxygen when flying even though no evidence of respiratory impairment is present. This is done for the reason that the patient with pneumonia already has endogenous anoxic anoxia and the addition of even a further slight anoxic anoxia as a result of his going to altitude may be sufficient to cause the patient grave trouble. The advisability of flying on the part of a patient with active pulmonary tuberculosis is in question; certainly if the lesion is more than minimal, the patient should not fly. The most important factor in a tuberculous patient's flying is whether or not he has a pneumothorax. The dangers to a patient with pneumothorax in traveling by air are numerous. Rapid contraction and expansion of the collapsed lung are deleterious to the healing process of tuberculosis. Tearing of adhesions attached to diseased pulmonary tissue may result in hemorrhage or in seeding the pneumothorax cavity with tubercle bacilli. Excessive compression of the lung may reduce the vital capacity seriously. Dowd⁹ reported the death of a patient with pneumothorax occurring as a result of transportation by plane at an altitude of 16,000 feet.

Persons with asthma should not travel by air during an acute attack and those

suffering from frequent severe attacks should not fly. The person with mild asthma may fly between attacks without difficulty.

Gastrointestinal ailments in crew members vary in importance according to the type of disease. Peptic ulcer, the most common chronic gastrointestinal disease found in pilots, varies in its importance according to the severity of the lesion. A pilot who has an acute peptic ulcer with pain and who is threatened with perforation or hemorrhage should not fly a plane. A pilot who has a healed or a chronic ulcer without symptoms may be able to fly without too great a risk. Certainly a pilot with any evidence of ulcer should be kept under observation for a time to determine the degree of severity of the lesion before being allowed to fly. A passenger with peptic ulcer can be transported with minimal risk except in a case of threatened perforation. In this case if the patient must be transported by plane, he should be flown at a low altitude to obviate the danger of increased intragastric and intraintestinal pressure due to the expansion of gases at increased altitudes. With the use of pressurized cabins in planes this danger will be entirely removed.

Gallbladder disease in a pilot should contraindicate his flying because of the danger that sudden acute colic might render him incapable of flying a plane. Gallbladder disease in a passenger in no way should interfere with plane travel any more than with any other form of travel. The severity of chronic diseases of the small and large intestine in the pilot will determine his ability or inability to fly. In the passenger these diseases are usually of little consequence in determining that person's risk in flying. A disease that is frequently overlooked and yet may be of very serious import in flying is acute gastro-enteritis in the pilot. This disease is of importance in the pilot because of its frequent occurrence and at times its acute debilitating affect which may so weaken the patient that he is incapable of carrying on his duties as a pilot. There have been incidents reported in which a pilot has been suddenly pros-

trated by acute gastro-enteritis with severe vomiting and diarrhea. The sudden exacerbation of the disease when the pilot is in a plane may be explained by the hyperirritability of the gastrointestinal tract induced by motion of the plane and the expansion of gastrointestinal gases which occurs at altitude. For the passenger this group of diseases is of little significance in so far as the ability to fly is concerned.

Genito-urinary diseases do not play an important part in aviation either from the standpoint of the pilot or the passenger unless they are severe. A renal or ureteral calculus is always a potential danger in a pilot because of the possibility of sudden severe colic and collapse. Gonorrhea in itself is no contraindication to a pilot's flying unless his general physical condition is so seriously impaired that he cannot properly carry out his duties in flying or unless the treatment for the disease might interfere with proper flying.

Active syphilis is adequate cause for suspending a pilot from flying until the clinical signs and symptoms have disappeared and until the patient is non-infectious and has been adequately adjusted to the disease and treatment. With the advances in the treatment of syphilis which have resulted from the use of penicillin and from more rapid treatment with the arsenicals and bismuth, these requirements can usually be met in four to six weeks. It must be emphasized that the serologic test for syphilis is not considered a test of efficiency of treatment or degree of activity of the disease except in early syphilis. Therefore, providing the patient has been adequately treated and there is no evidence of active syphilis, the results of the serologic tests may be ignored in determining the qualification of the person for flying. Syphilis in a passenger does not contraindicate flying unless the disease is in an infectious stage.

Diabetes mellitus of even mild degree occurring in a pilot should be cause for permanent grounding because of the dangers of diabetic coma and hypoglycemic reaction. Observations on passengers with

diabetes mellitus have revealed no serious effects from flying. Hyperinsulinism from any cause is a definite danger when it occurs in a pilot. Hyperthyroidism or hypothyroidism of such a degree as to be clinically evident is a contraindication for a career of flying; either disease in a passenger should in no way interfere with his flying.

Diseases of the skeletal system, such as various types of arthritis, residuals of poliomyelitis and fracture deformities, are to be judged solely by the amount of mechanical interference present in the person handling the controls of a plane.

Aerial transportation of patients who had intracranial injuries was accomplished by the armed services without adverse effect. In order to combat the anoxia of brain tissue associated with increased intracranial pressure, oxygen should be administered from the ground up during flight. Encephalography or ventriculography within the past seven days or any condition in which intracranial entrapment of air is demonstrated is a contraindication to travel by air.

The psychotic patient should not be transported by air because of the difficulty in controlling him on a plane and because of the potential danger that he may get out of control and do damage to the ship and crew. There is no contraindication for the psychoneurotic patient's flying except that these patients are usually more prone than usual to suffer from airsickness.

The patient with severe anemia is already suffering from an anemic anoxia. If that patient is taken to high altitudes, an anoxic anoxia is superimposed and the patient may evince clinical signs of anoxia. Thus the severely anemic patient should receive oxygen on flying to prevent this complication. The slightly anemic patient can usually be transported by air without difficulty because the anemia anoxia is so minor.

SUMMARY

The technical advances in aircraft are lessening the number of medical contraindications for flying. The increased efficiency of oxygen systems and the increasingly extensive use of such systems has made it safer now than formerly for the patient with hypoxia to fly. This includes the patients who have respiratory illnesses, severe or complicated cardiac disease and anemia. The use of pressurized cabins in aircraft will obviate the precautions now necessary in transporting patients who are suffering from conditions that would be made worse by the expansion of intra-abdominal or intrathoracic gas which occurs in unpressurized aircraft. Also, as people become increasingly accustomed to transportation by air and as such transportation becomes increasingly safe, there will be a decrease in apprehension and thus in nervous stimulation, with its side effects, for the individual in flying.

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Neuropsychiatric Problems of the Flyer

R. C. ANDERSON, M.D.*

Topeka, Kansas

EXPERIENCE of neuropsychiatrists with flying personnel in World War II has served to establish the fact that the neuropsychiatric problems of such personnel are the same as those which occur in all other environments. The causative agents are the same and the end result is the same. Such a statement may seem superfluous at first glance but it has not always been generally accepted. This is because of the fact that during the development of aviation medicine there was a tendency for medical men to describe entities of disease occurring in flyers largely in environmental terms. This disposition resulted in a fairly widespread belief that many conditions were wholly peculiar to flying personnel. This tendency was probably more marked in the field of neuropsychiatry than in some others. Most of the pioneers of aviation medicine were not primarily interested or qualified in neuropsychiatry. Hence the early flight surgeon was not familiar with neuropsychiatric disorders occurring in any environment. Those that he saw occurring in flyers were described and thought of as distinct and new entities.

This tendency was productive of such terminology as aeroneurosis, aero-asthenia, flying fatigue and so forth. These conditions were described by Armstrong¹ and others quite early. As trained neuropsychiatrists began to take a part in aviation medicine they recognized that all of this terminology was composed of new names for old friends—the various neurotic reactions. This viewpoint was not greeted with enthusiasm or wide acceptance at first by the majority of those interested in either aviation or aviation medicine. The term “neurosis”

carried a certain stigma which both the aviator and the doctor were loath to associate with the highly selected individual who was the peacetime flyer.

While World War II afforded an increased opportunity for the consideration of neurotic reactions in flyers, it also afforded a further opportunity to avoid distasteful terminology. The term “war neurosis” came into widespread use and as applied to flying personnel was known as “operational fatigue.” This term not only implied a condition peculiar to aviation but also to combat or operational flying. Actually it was no more peculiar to flying than to any other activity accompanied by the same type and amount of stress and it was likewise not peculiar to combat. Grinker and Spiegel² have recently stated that war neuroses (including operational fatigue) are in reality psychoneuroses.

The peacetime aviator develops the same type of neurotic disturbances as does the combat flyer and for the same reasons. The incidence is less in the peacetime aviator because the quantity of stress is less and the individual is more highly selected. Too much emphasis should not be placed on this last factor however. Selection as nearly perfect as is possible will not guarantee that the individual will not be subjected to intolerable stresses resulting in a neurosis. Obviously the possibilities for such stress situations are greater in an environment with the admitted and ever present dangers of aviation than in most other peacetime environments.

The causative agent of the neuroses of flyers is anxiety as is true of all other neuroses. The individual method of expression of that anxiety determines the form of reaction presented by the patient. This

* Former Chief of Psychiatry, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

allows for a wide variation of syndromes and symptom complexes. However, allowing reasonable latitudes there are certain general reaction types which occur more frequently than others in flying personnel. One feature which tends to distinguish the neuroses of the flyer from those of the average individual is the strong conscious component which is usually present. Often this conscious element is the presenting one, such as "I'm scared to fly." The doctor not trained in neuropsychiatry is apt to call such a condition simple "fear" and to overlook its true meaning and significance. These facts have been nicely described by Bond.³

TYPES OF REACTIONS

Phobias. Of all the neurotic disorders to which flyers are subject by far the most common is phobia. Not only does this phenomenon occur alone but in many instances in which other syndromes predominate phobic manifestations are accompaniments. A phobia is defined as a morbid fear of a specific situation or thing. The student of psychopathology knows, however, that such a symptom may be a clever disguise for the true underlying situation. This is especially important to bear in mind in the phobias of flyers.

The conscious expression and presenting symptom of the flyer's phobia usually takes the form of a fear of flying a particular type of aircraft, or more rarely all aircraft, a fear of a particular type of flying such as night flying and fear of flying over certain types of terrain. Superficially it seems that an isolated activity has been made the focus of conscious anxiety. This is true but what is equally true, and often overlooked, is that the same activity is the focus of a great deal of anxiety concerning the origin of which the individual is unconscious.

Such a patient is usually able to regard his symptoms objectively. However, he finds that the amount of anxiety which is attached to the specific focus is out of all proportion to his conscious desires and beyond his conscious understanding. The patient can give no reason why flying which

was formerly a pleasure has now become a source of unreasoning fear. The conscious expressions of fear which such a patient offers are in reality just as much "conversions" as are the more dramatic symptoms of hysteria. The only difference is that the symptom is expressed mentally instead of physically.

Very often the fatalistic attitude which most experienced flyers adopt sooner or later resolves itself in the conviction that death in an airplane is inevitable. If the flyer is subjected to a series of minor escapes from death or considerable time clapses, this conviction may be unconsciously expanded to include the premise that each flight will be the last. Often identification with a dead friend who was "a better pilot than I" may strengthen this conviction. The flyer takes off on every flight unconsciously saying to himself in the best Hollywood fashion, "This is it."

As such a situation as that described continues, the flyer builds up an enormous amount of anxiety about the true origin of which he is unaware. The fact that something does not happen to him becomes more disturbing in effect than if something did. The next step is the displacement of this anxiety to some isolated activity and thus the phobia results. The mechanism of displacement is frequently utilized by the neurotic flyer and it, together with identification, accounts for most of his difficulties.

Perhaps more rarely the true origin of the phobia may lie in the flyer's interpersonal relations. Thus he develops an aversion to a particular type of plane in order that he may be moved from an organization in which there is some individual particularly distasteful to him. The underlying emotion of hate is not consciously experienced in such an instance any more than is the true fear from which the individual in the first group suffers.

That a large part of the phobia is unconsciously motivated is attested by the tendency for such reactions to "spread." Once the pilot has a definite phobia for a particular type of aircraft his symptoms are usually

not long alleviated by being removed from that aircraft. The phobia encompasses succeeding types of airplanes, succeeding types of flying and so forth, and becomes more and more crippling as time progresses. Because of these characteristics the prognosis is relatively bad in such a reaction.

The phobias are usually stubborn and resistant to treatment. The underlying emotions are firmly repressed and it is difficult to bring them to light and develop true insight. If the patient attempts to carry on as a flyer in the face of his phobia, he may have psychosomatic symptoms as secondary expressions of his repressed emotions. "Tension headaches," vertigo and so forth are the most common of these. Such patients are prone to carry on as long as possible since they suffer from the same fallacy of conscious reasoning that the observer may, and do not wish to admit "cowardice." Such a patient may be quite comfortable and symptom-free if not exposed to the precipitating stimulus. This is characteristic of all phobias. Thus the flyer may have no further difficulty if he renounces flying but obviously this does not constitute a cure.

Anxiety Reaction. Although phobia formation constitutes one of the most frequent neurotic symptoms of the flyer, the syndrome designated "anxiety state" or "anxiety reaction" is the most common generalized manifestation. Various phobias may form a part of this picture but in the anxiety reaction the disturbance of the personality is more widespread than in simple phobia formation.

It is the anxiety reaction which formed the major part of conditions known as "operational fatigue" in combat flyers. However, it can and does occur in non-combat flyers. Classically, it may be the result either of long-continued minor stress or a single overwhelming experience. The opportunities for the latter are somewhat greater in combat, but it is important to bear in mind that the peacetime aviator is subjected to long-continued minor stress.

Characteristically, this reaction takes

place in a series of steps denoting its increasing severity of manifestation. The first of these steps is usually disturbances of sleep. In the beginning this takes the form of difficulty in going to sleep. The patient who has been able to dissipate a portion of his anxiety and tension in activity during the day is unable to do so in the quiet immobility and darkness after going to bed. Consequently his anxieties seem intensified at this time and he is unable to relax and go to sleep. When sleep is finally attained, the next disturbance is in the form of dreams. These are occupational in nature and usually involve the patient in frightening accidents and emergencies. He dreams of crashes, of stalling out and catching on fire. Also common is dreaming of unsuccessful attempts to land the airplane. These dreams are often accompanied by talking and even walking in sleep and also may awaken the patient. All of these phenomena interfere with rest as they persist and increase so that the patient has the burden of physical fatigue added to his other difficulties.

The next step in the development of the anxiety reaction is the appearance of states of partial dissociation of consciousness in the daytime. Partially as a result of his disturbed rest the patient is apt to be subject to drowsiness in the daytime. In severe cases this may produce the "startle reaction" to sudden stimuli. Also, as the anxiety increases the patient logically becomes introspective and preoccupied with his thoughts and his problems which results in a partial detachment from his surroundings.

The next step is the appearance of a personality change. This is due to the patient's realization that something is wrong and his inability satisfactorily to explain it as the result of his introspection. The personality change follows no set pattern but usually takes the form of expression of characteristics which are opposite to the patient's usual personality. Prominently associated with this is depression of mood, which may be severe in degree, and extreme irritability. The latter may be the most prominent feature to the casual observer.

The patient is also self-conscious and may develop mild ideas of reference, believing that others are "watching" him, and so forth.

Accompanying all this are the usual somatic concomitants of anxiety. The patient experiences palpitation of the heart, dyspnea and urinary frequency. Loss of appetite is common and contributes to loss of weight. Objectively the patient shows coarse tremors. The use of tobacco and alcohol may become excessive.

The success of treatment of this condition varies with the stage in which it is recognized. In common with all neurotic disorders the earlier treatment is begun the better is the prognosis. If the condition is recognized in the earlier stages of disturbances of sleep and fatigue, excellent results may be obtained by temporary respite from flying duties, sedation and simple explanation and reassurance. Beyond this stage psychotherapy must be much more intensive and results are not nearly so encouraging. The most common mistake which is made is to expect that grounding the patient will relieve the symptoms of a fully developed and long-established neurosis. Simply removing the stimulus does not alter such behavior patterns once they are firmly established and this fact has been a source of disappointment and misunderstanding to the patient and physician alike. Rest alone does not cure neuroses.

Reactive Depression. As indicated in the preceding section reactive depression may be a symptom of some of the other types of disturbance. However, more rarely this may be the predominant reaction. The depth of depression may be great and it may be difficult to distinguish from a true depression.

The more severe forms of reactive depression in flying personnel are usually the result of identification with dead friends or the assumption of responsibility for the death of others in crashes and collisions. Very often the true underlying cause may be repressed hostility toward those who are dead. In the opinion of this writer, however,

such ambivalence is not necessarily present and straight identification can occur without it.

The individual who has identified himself with a dead friend or associate may arrive at the same conclusions regarding the inevitability of death in an airplane as was described in the discussion of phobias. Instead of a phobia a profound depression may develop as the result chiefly of his own personal characteristics. Those who develop depressions in such circumstances are usually somewhat immature and narcissistic in their personality make-ups. I have seen several such patients in whom a lifelong phobia of death itself was accompanied by childish fantasies of never growing old or never getting sick.

The patient with a moderate reactive depression is frequently overlooked by his lay associates and sometimes by the physician. This is especially dangerous because the retarded psychomotor processes of such an individual may constitute a real menace to the safety of himself and others if he continues to operate an airplane. Careful investigation should be made of those flyers who are often described as having lost interest or being difficult to deal with. Patients with severe cases are usually recognized easily. The patient shows a facies of hopelessness, retardation of thought and activity and has loss of appetite, sleeplessness and so forth. Overlooking a patient with reactive depression or forcing the aviator so affected to fly may result in suicide. The airplane is a convenient instrument of self-destruction which may explain some "unexplained" crashes.

Fortunately this group of patients probably responds better to treatment than any of the others if that treatment is prompt and intelligent. It goes without saying that the patient must be temporarily suspended from flying duties. He then must be given insight into his identifications, and the lack of logic for his assumption of responsibility for matters entirely beyond his control must be pointed out. This type of patient is always wholly unconscious of these matters. If the

patient is intelligent and the therapist is skillful, the response to this type of management is dramatic. The patient may show an almost complete reversal of attitude in a short time.

Neurasthenic Syndrome. Prominent among the neurotic disturbances of flyers is the neurasthenic syndrome. This is the result of displacement of anxiety arising from other sources to the focus of physical symptoms. The neurasthenic flyer does not differ clinically from his counterpart in any other activity but, as has been pointed out, the environment of flying itself may provide him with some anxiety which he may choose to handle in this manner. The neurasthenic type of reaction tends to be insidious in onset and consequently is not usually seen as the result of one or two severe traumatic experiences. Rather, it develops gradually as the result of minor and long-continued stress. It is important to bear in mind that the responsible factors may be wholly unrelated to flying.

The neurasthenic syndrome is usually the response of individuals who are unhappy and dissatisfied with their environment in general. Many flyers learn that their profession is not all glamour but are either unprepared for other activities or unwilling to admit failure. They may express the anxiety arising from this situation as anxiety concerning their physical health. Their symptoms are of the hypochondriacal type familiar to every physician.

The symptoms of the neurasthenic flyer in themselves do not prevent him from flying. Usually he expresses himself as believing that he should not fly until they have been alleviated, or that he cannot be expected to fly efficiently feeling as he does. No anxiety is ever expressed directly related to flying. The patient is perfectly willing to fly and desires to fly even if he is told that this is inadvisable. The only concern which the patient expresses is in regard to his health and he is persistent in his efforts to improve it. Often in flyers the symptoms may take the form of exaggerating physical defects. Thus the mild sinusitis becomes

worse, there is increasing difficulty in clearing the ears and so on.

All neurasthenic patients are relatively recalcitrant to treatment and flying personnel is no exception. The reaction is usually related to deeply-seated personality traits which are difficult to modify. Successful treatment of any neurasthenic usually involves an extensive alteration of the patient's environment. If the flyer's difficulties do not stem from flying itself, this may be accomplished. If the patient's basic difficulty is flying, he cannot be successfully treated as a flyer. Those patients in whom actual organic defects are exaggerated are especially difficult to deal with. A word of caution is in order concerning the symptomatic treatment of the neurasthenic patient. This is frequently done and results in the physician's literally "chasing" the symptoms all over the patient's body. The patient may be expected always to remain one step ahead of the treatment by the mechanism of displacement. Some neurasthenic flyers may continue to function somewhat inefficiently as flyers in peacetime aviation. Obviously this is not desirable from the viewpoint of either the patient or others.

Conversion Phenomena. Hysterical conversion phenomena of the dramatic and obvious type usually described are not too common in flying personnel. It is generally recognized that these phenomena have had a decreasing incidence in general for the past several years. An occasional flyer, particularly the neophyte, may develop the classical paralysis or anesthesia identified with hysteria but this is relatively rare. During the war a few cases of hysterical amblyopia were reported including a case in which a totally "blind" cadet was safely guided to a landing.

It has been established fairly recently, however, that flying personnel do present a fairly large number of conversion phenomena which are much more obscure and can be detected only by painstaking investigation in many instances. These are chiefly related to the special senses and are often of a type which do not totally in-

capacitate the flyer but protect him from special types of flying. From the beginning of aviation sufficient medical emphasis has been placed on the senses of sight and hearing for their importance to be thoroughly appreciated, and perhaps overestimated, by the flyer. Hysterical symptoms referable to these functions therefore are quite logical.

Such symptoms usually take the form of mild impairment of visual acuity, depth perception, night vision or hearing. Diminution of visual acuity is a common response to an aversion for instrument flying. The weakened eyes cannot tolerate the strain of continued observation of instruments. Similarly, disturbances of depth perception are utilized as protection against formation flying and to explain poor landing techniques. Defective night vision protects from night flying. Many cases of "aviation deafness" occurring in young flyers with only 300 or 400 hours of flying experience are hysterical in origin. Often they do not bother the individual except with reference to the intercommunication system. Thus he cannot instruct and communicate with his student, he cannot fly multiplaced ships and converse with his crew. Defective hearing is also utilized to protect from instrument flying and in many instances the flyer can hear everything perfectly with the sole exception of the radio "beam." Very few such patients are malingerers as might be expected. The deception of the true malingerer is not readily exposed and is not influenced by suggestion as are the symptoms of these patients. As is characteristic in all cases of hysteria the patient accepts his disability philosophically and is anxious to carry on as best he can in the presence of the impairment.

Symptoms of this type are amenable to treatment as far as their removal or improvement is concerned and respond readily to simple suggestion and reassurance. However, this in no way guarantees against their recurrence or the substitution of new symptoms. Consequently, for the flyer who has this type of reaction the prognosis for future usefulness in flying is guarded. In

peacetime aviation it may be possible to assure that such a flyer need not participate in those types of aviation distasteful to him.

Psychosomatic Disturbances. This is a group of conditions often confused with conversion phenomena. In these conditions, however, the symptoms do not represent the conversion of anxiety into the physical symptoms of hysteria. Instead, they represent the individual's expression of anxiety through lower visceral centers. One of the best descriptions of this group of disturbances has been given by Grinker and Spiegel.²

Recognition of psychosomatic diseases has increased greatly as a result of the war just concluded. By and large they formed the largest problem with which the military physician had to deal. The visceral system most often disturbed was the gastrointestinal system and if one considers the early steps of personality development the use of this system by the patient to express emotion becomes quite logical. Most of the "dyspepsias," "ulcer syndromes" and so forth seen in American troops had their origin here. This fact was also recognized by our enemies although their understanding of the etiology may have been imperfect. The surgeon of the German Luftwaffe is quoted as having said, "The psychological diseases of World War I become physiological diseases in World War II. The soldier who had an hysterical paralysis in World War I, vomited in World War II."⁴

With reference to the flyer this group of disorders is probably of most significance in relation to so-called airsickness. It is not meant to imply that airsickness, or preferably motion sickness, does not exist on an etiologic basis which is chiefly physiologic. A few simple experiments with exposure to the effects of motion will convince the most confirmed skeptic of that. In common with most disturbances of the human organism, however, this is one in which it is most often impossible to draw a hard and fast line between the psychic and somatic factors responsible. About the most that can be hoped for is to determine which factor seems to predominate in the given case. There are

many cases of airsickness in which the psychic factor predominates to the extent that the physical one is of negligible importance.

In many cases of airsickness it can be readily demonstrated that there is little or no relationship between the symptoms and motion or other purely physical factors. This includes those patients in whom vomiting is precipitated by the sight of an airplane or begins before the plane is air-borne. The fact that some of these patients respond to various motion sickness preventatives does not alter the basic premise. Most of these remedies are composed of sedative drugs in various combinations. Many experienced flyers who are ordinarily not susceptible to motion sickness recognize the fact that they are more apt to be susceptible if they are "nervous" or worried about something. Some cases of airsickness may represent conversion phenomena but ordinarily the hysterical patient does not choose symptoms so disagreeable and prostrating as these. Occasionally the flyer may be subject to diarrhea just prior to flights or after their conclusion. This is another way in which the gastrointestinal tract "speaks." The writer has seen one high-ranking flyer officer of long experience in whom this was a regular phenomenon.

The treatment of these disturbances follows that of all other psychosomatic complaints. Most important is the recognition of the true underlying etiology. Intelligent patients under skillful therapists make excellent recoveries in many instances following the development of insight. As in all other forms of psychotherapy much depends upon the therapist, the transference he can establish and the reassurance he can give. In military aviation the time involved in dealing with such patients is usually not available as a routine procedure. In the case of the peacetime flyer and in key personnel it might be.

SUMMARY

The foregoing constitutes a general description of the psychiatric ills to which the

flyer is heir. It is easy to recognize the fact that leaving the earth for the alien environment of the atmosphere produces no new syndromes. The individual personality continues to react with its environment in much the same ways regardless of what the environment may be. Some environments may contain more situations of stress and hence be productive of a relatively higher incidence of neurotic reactions than are others. The individual's response to stress tends to be the same regardless of where he may be. Since this is true it goes without saying that the neuropsychiatric problems of the peacetime aviator are qualitatively the same as those of the combat flyer. Quantitatively there may be some difference.

The most important point to bear in mind is that the best treatment of these reactions is prophylaxis. In war this is vastly more difficult than in peace. All flyers should be assured of adequate rest and relief from flying duties so that they do not become "stale." Adequate recreational outlets for the increased tension borne in the air must be provided and encouraged. Early symptoms of impending neurotic disorders and psychosomatic disturbances must be promptly recognized, their basic origin determined and appropriate psychotherapy begun before irreversible behavior patterns are established. The physician must be aware of the potentialities present and not be content to give the patient ever changing symptomatic treatment. In short, the intelligent management of the neurotic flyer is the same as the intelligent management of all other neurotics. It follows that the procedures of mental hygiene are also the same.

A final word of warning is in order concerning an old fallacy that all neurotic disorders might be prevented in flyers and others by proper selection of personnel. The experience of the war has shown this not to be true. This is because even the most stable and well adjusted personalities do not represent perfection. Consequently there is always a weak spot in the personality armor which may succumb only to a specific stress to which it is sensitive. It is

impossible to predict whether or not the individual will be exposed to the specific stress he cannot tolerate. In some of course the weak spot is large. In others it is small. So-called predisposition is important, therefore, in a quantitative sense but to a considerable degree all individuals are predisposed.

Another fallacy exploded by the war is that the known neurotic cannot fly successfully. Hastings, Wright and Glueck's⁵ report of 150 successful combat pilots, 50 per cent of whom had histories of pre-existing instabilities sufficient to be considered evidence of neuroticism by most standards, serves to emphasize this point. In many cases flying itself may afford the individual relief from his basic conflicts

and an outlet for his basic anxieties. This is not meant to imply that neuroticism is a favorable characteristic. All things being equal the efficiency of the non-neurotic is likely to be greater than is that of the man who starts any activity with a neurosis already established.

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Use of Drugs at High Altitude

PAUL K. SMITH, Ph.D.*

Washington, D.C.

IT is important to determine if drugs frequently employed in aviation medicine act differently at high altitudes. Modification of action under such conditions might occur because of diminished barometric pressure, partial anoxia or extreme cold. Various attempts have been made to use drugs to improve altitude tolerance and to relieve the pain of decompression sickness. Evidence is lacking that many substances actually increase altitude tolerance. It is unlikely that any drug will be more than moderately effective so far as intensity or duration of action is concerned. During the war emphasis was placed, almost certainly correctly, on improvements in oxygen equipment rather than on temporary and uncertain measures designed to enable men to get along with unsatisfactory equipment.

Various dietary factors have been given considerable attention in the belief that such measures would be more lasting and physiologic. It is suggested from studies of visual¹ and psychomotor² performance that the ingestion of large amounts of glucose will improve performance under hypoxic conditions. There is some evidence that a low blood sugar interferes with oxygenation of the central nervous system^{3,4} so that a simultaneous mild hypoxia and hypoglycemia produce symptoms similar to those associated with severe oxygen lack and normal blood sugar. This may be justification for supplying foods rich in carbohydrate to personnel immediately before they fly to high altitudes.⁵ Experimentally 50 Gm. or more of glucose has been employed with moderate improvement in performance.¹

Some time ago it was reported that ani-

mals on a carrot diet were more resistant to the lethal effects of hypoxia than animals on an ordinary diet.^{6,7} This has been confirmed⁸ but when a loss of reflex response or electroencephalograms were used as criteria⁹ no improvement was noted. So far no dietary factor other than glucose has been demonstrated to be of definite value.

Experimentally, subconvulsive doses of apomorphine, camphor, tetrazol, potassium cyanide and strychnine have all been shown to protect against the lethal effects of anoxia in mice but the respiratory stimulating effect may have been the most important factor.¹⁰ Under similar conditions full narcotic doses of ethyl alcohol are effective, perhaps through a general reduction in metabolism with a subsequent diminution in oxygen requirement.¹¹ Anesthetic doses of amytal or of pentobarbital sodium were not beneficial but moderate doses¹² of diphenylhydantoin sodium gave some protection. Further studies of agents affecting the autonomic nervous system¹³ revealed that cholinergic and sympatholytic drugs protected against the lethal effects of acute anoxia in mice but adrenergic agents increased the lethal effects. In general, drugs which increase the metabolic rate, such as thyroxine and dinitrophenol,¹⁴ diminish hypoxia tolerance.

Several studies have shown that the adrenal cortex is involved in some manner with tolerance to oxygen deficiency.^{15,16} During the initial phase of anoxia the blood sugar is normal and the amount of glycogen stored in the liver is diminished. This may result from an increased utilization of carbohydrate. Further adaptation to anoxia involves increased protein catabolism with a rise in carbohydrate stores and an increase

* Former Chief of Pharmacology, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

in urinary nitrogen. These changes did not take place in the absence of the adrenal cortex and injections of adrenal cortical extracts¹⁶ greatly increased the survival rate. Desoxycorticosterone acetate and 17-hydroxycorticosterone were ineffective. In spite of the promising experimental evidence of effectiveness there are no clinical data to justify the use of cortical extracts to increase hypoxia tolerance.

Since carbon dioxide is such an effective respiratory stimulant, several attempts have been made¹⁷⁻¹⁹ to utilize it to increase anoxia tolerance. Its effectiveness has not been established with certainty but the ultimate result seems to depend on whether or not the inevitable reduction in alveolar oxygen tension is more than compensated by increased minute respiratory volume, cerebral vasodilatation and shift in the oxy-hemoglobin curve.

Under conditions of partial anoxia certain analeptics such as benzedrine, desoxyephedrine (methedrine) and caffeine improve psychomotor performance.^{9,20,21} There is some evidence that benzedrine is superior to caffeine for this purpose. Whether or not a mild respiratory stimulating effect of the drugs could be responsible for the result is not known.

DRUGS ALLEGED TO REDUCE HYPOXIA TOLERANCE

It has been important to determine whether or not certain drugs sometimes administered routinely to flying personnel, such as the antimalarial drugs and the sulfonamides, diminish altitude tolerance. This has presented problems of measurement of great complexity since it is insufficient to know merely that such drugs do not of themselves endanger life at high altitudes, but whether they interfere in any way with the most efficient performance of duties. Obviously only study of human subjects is satisfactory and this requires careful evaluation of such factors as adaptation, learning and motivation. These problems have been partially solved by the use of multiple psychomotor tests.²²

Because of the use of sulfonamides in ambulatory patients, several studies have been made of the effects of these on the performance of certain tasks. If anemia or methemoglobinemia is associated with the administration of a sulfonamide, there is little doubt that hypoxia tolerance is reduced. This rarely occurs, however, except with sulfanilamide and since clinically this drug has been replaced by less toxic ones the danger from such an effect is small. Moderate doses of sulfanilamide affected an adversely psychomotor performance²³ but under similar conditions sulfathiazole and sulfadiazine were without effect. However, some studies of sulfathiazole and sulfadiazine show that visual depth perception and the muscle balance of the eyes is affected²² although no differences in mental efficiency or hand-eye coordination were observed.^{22,24,25} Tests at simulated altitudes^{22,26} have failed to show any decrement in psychomotor performance with either sulfadiazine or sulfathiazole.

The antimalarial drugs have been widely employed in suppressive doses and it has been necessary to determine carefully whether or not they interfere with flying efficiency. Many of the toxic effects of quinine, such as visual and auditory disturbances, will obviously interfere as will the irritating effects of quinacrine hydrochloride (atabrine)²⁷ on the gastrointestinal tract, but more attention has been directed to determining if reduction in oxygen tension will accentuate these effects or introduce new ones. Fortunately quinine, atabrine²⁷ and chloroquin²⁸ are not demonstrably more toxic at 18,000 feet simulated altitude than at ground level.

Because of the frequent use of morphine in battle casualties and its known ability to depress respiration, studies have been made to determine if the toxic effects of morphine are enhanced at high altitudes. One early study on mice²⁹ revealed a marked increase in fatality rate; all animals who received morphine died at 27,500 feet and all controls survived. Other studies on human subjects have revealed no serious

respiratory depression^{30,31} although maintenance of blood oxygen varied in different subjects. It was somewhat diminished in those subjects whose reflex excitability was poor.

RELIEF OF DECOMPRESSION PAIN

Little progress has been made in the search for drugs for the relief of decompression pain. Because of its respiratory depressant effects, there is some hesitancy to use morphine but a more serious objection is its relatively slow onset of action³¹ in a condition which frequently will lead to serious collapse. Certain, more rapidly acting analgesics are suggested and some preliminary studies in which an ampule of trichlorethylene was crushed in the oxygen inlet showed that it had promise as an analgesic, but it occasionally gave rise to cardiac disturbances and it should be used with caution if at all. A 20 per cent mixture of nitrous oxide is known to be a good analgesic³² but such a mixture with oxygen may be explosive. The synthetic analgesic, demerol, is almost as slow in its action as morphine after subcutaneous administration.

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Treatment of Airsickness with Drugs

PAUL K. SMITH, Ph.D.*

Washington, D.C.

AIRSICKNESS is a form of motion sickness to which most people probably are susceptible depending on the duration of flight, type of plane, position in plane and the weather as well as other undetermined factors. Certain factors, such as apprehension and fear, are believed by some to be more important in airsickness than in other forms of motion sickness. Air passengers in both military and civilian life may have had but little flying experience or may fly so infrequently that adaptation does not occur. It is in this group that drugs may be of greatest value. Studies in the air forces have shown that the incidence diminishes rapidly with experience in the air.¹

The movement of aircraft is highly erratic and depends on the type of aircraft and the weather conditions to so large an extent that other devices have been used for producing motion sickness. The most widely employed has been the simple swing.² Others have included vertical accelerators³ and rotating chairs.⁴

A drug for the relief of airsickness should prevent airsickness without producing any other pharmacologic effects. It should be active after oral administration and the onset of action should be immediate. It should not be toxic, habit-forming or cause disagreeable symptoms. At present remedies are available which will decrease the incidence of airsickness to about one-third without producing appreciable side effects. In general the drugs used have been those that have been employed in seasickness or drugs related to these. Most of them are either central nervous system depressants such as barbiturates, central nervous system stimulants such as benzedrine or para-

sympatholytic agents such as drugs of the atropine series. Various criteria have been employed in evaluating the remedies but in general vomiting alone as the chief criterion is usually the most reliable.

It is surprising that many studies have been made on motion sickness with mixtures of drugs without first determining the effectiveness of the component drugs. Frequently the central nervous system stimulants have been incorporated to prevent undue depression and in some as many as seven different drugs have been employed simultaneously.⁴

The most promising group of drugs have been those with parasympatholytic action such as atropine and related drugs. Of those of demonstrated effectiveness, atropine, hyoscyamine and hyoscine (scopolamine) are the most effective. On the basis of their effect on motion sickness alone there is not much difference between these three drugs. However, it has been demonstrated that the suppression of salivation is less with hyoscine than with atropine or hyoscyamine when they are all used in effective doses.⁵ For this reason hyoscine has been employed most frequently although there is little evidence that it is actually superior in its ability to relieve motion sickness. It has been shown to be effective in seasickness,⁶ swing sickness⁷ and airsickness.^{8,9} The doses that have been employed most commonly are 1.0 mg. of atropine sulfate or of hyoscyamine hydrobromide or 0.65 to 0.75 mg. of hyoscine hydrobromide. The onset of action after the oral administration of the drug is not very rapid, about one hour being required for an appreciable suppression of salivation. The actual duration of action of these drugs is not known but there

* Former Chief of Pharmacology, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

is some evidence from studies on swing sickness that the effectiveness lasts for approximately six hours.

The central nervous system stimulants that have been employed include ephedrine, benzedrine and methedrine (desoxyephedrine). There is not sufficient evidence to justify the belief that they are effective remedies for motion sickness, either alone or when incorporated with other substances. These drugs are usually used in combination with central nervous system depressants in an attempt to prevent undue depression without detracting from the effects of the drugs on motion sickness.

The barbiturates are of particular interest because many of them had been incorporated in drugs for treatment of motion sickness and have been widely employed without definite knowledge of whether the barbiturates themselves contributed anything to the effectiveness of the remedy. In the opinion of some¹⁰ the action of the barbiturates and thiobarbiturates in motion sickness is not related to the depressant action on the central nervous system. Several barbiturates have been studied including the long-acting ones such as sodium barbital and phenobarbital and the shorter-acting ones such as amytal, pentobarbital sodium and seconal. Although occasionally some studies have shown them to be partially effective, a careful review of the results obtained reveals that their use in treatment of motion sickness¹¹ is not justified.

The thiobarbiturates have been studied for the relief of motion sickness because of the possibility that these compounds, many of which have been known to produce actual central nervous stimulation, would be effective in motion sickness yet not produce undue depression. Noble, in the Canadian laboratories, has studied several of these and one of them, ethyl- β -methylallyl thiobarbituric acid, was shown to be moderately effective in swing sickness.¹⁰ Later studies of seasickness and swing sickness^{12,13} did not reveal such dramatic results. This thiobarbiturate has a long-continued action and Noble has stressed the value of pre-

treatment with the drug. This of course would impair its usefulness in airsickness.

Several vitamins have been employed experimentally for the relief of motion sickness and some of them have been incorporated with other drugs. Because of its dilating effect on cerebral vessels, niacin (nicotinic acid) has been employed in mixtures in an attempt to increase the concentration of alkaloids in the cerebral circulation. Some early results in swing sickness led to its adoption as one of the components of the Canadian seasickness remedy, but later studies have failed to confirm the beneficial effects¹⁰ and it is now generally believed that it has not contributed to the effectiveness of this remedy. Thiamine has been demonstrated to be without appreciable effect in swing sickness.¹⁴ Pyridoxine has been used in the treatment of nausea and vomiting of pregnancy^{15,16} and the nausea and vomiting associated with radiation sickness.¹⁷ This led to its study in swing sickness but it was not demonstrated to be effective.¹⁸

In an attempt to overcome the depressing effects on salivation of atropine-like drugs, neostigmine bromide was employed in combination with hyoscine,¹² atropine¹³ or syntropan.¹³ In no case was the observed protection increased appreciably by the neostigmine.

Many of the drugs proposed for use in airsickness may produce, when given in large doses, sufficiently severe side effects to preclude their use by personnel other than passengers. Of the atropine-like drugs the principal effect is dryness of the mouth associated with the decrease in flow of saliva. This occurs to a significant extent with the more effective atropine-like drugs although the depression of salivary secretion is not closely associated with the effectiveness of the drug in swing sickness.⁵ In a study of performance, in which addition and decoding tests were used for testing intelligence and pursuit meters and steadiness tests for testing psychomotor performance, no significant effects were observed after the administration of 0.5 mg. hyoscine hydrobromide⁷ either at ground level or at

18,000 feet simulated altitude. Although the near point of accommodation was not affected by any atropine-like drugs in the doses commonly employed, Keil has shown¹⁹ that doses of hyoscine greater than 1.5 mg. produce effects on accommodation and significantly lower visual efficiency in many individuals. Administration of a dose of 1.5 mg. or more would correspond to the simultaneous administration of more than two of the commonly employed doses of hyoscine. Significant deleterious effects on vision were not observed in navigation students either in the Navy⁸ or the Army Air Forces⁹ when hyoscine was employed for airsickness. These are rather critical groups for such a study since they fly rather long missions and during most of the time are working on charts and instruments that require good near vision. In another study of possible side effects of hyoscine that might be of importance it was found that neither hyoscine nor hyoscyamine had any obvious effect on physical performance, ability to shoot¹³ or near vision. Other studies have shown that hyoscine is unlikely to have any deleterious effect due to diminution of sweating unless given to men on the border line of heat stroke.⁶

As is to be expected the ordinary barbiturates may produce considerable central nervous system depression although the doses ordinarily employed are smaller than those commonly used for hypnosis. In a comparative study of the Royal Canadian seasickness remedy (containing hyoscine, hyoscyamine and niacin), the army motion sickness remedy (containing hyoscine, atropine and niacin) and hyoscine alone¹³ the effects were placed in two categories: those in which the subjects complained of a hot, dry feeling, dry mouth and blurriness of vision and those in which the primary sensation was that of being doped or drugged with the most common complaint being sleepiness. Most of the complaints of those taking the Canadian seasickness remedy were of the second type with the fewest complaints being made by the group taking hyoscine alone.

An analysis of the effects of drugs on motion sickness suggests that central mechanisms at a cortical level are of no greater importance in airsickness than in other forms of motion sickness. Evidence for this is: (1) the correlation between the effects of various drugs in swing sickness, seasickness and airsickness; (2) the lack of effectiveness in any type of motion sickness of cortical depressants such as barbiturates and chlorobutanol; (3) the failure of epinephrine to increase the susceptibility to motion sickness and (4) the lack of evidence that drugs effective in motion sickness are depressants of the central nervous system. In connection with the last it is common to suppose that hyoscine is a depressant of the central nervous system although in therapeutic doses it is a respiratory stimulant. The evidence on this point is incomplete but observations that mixtures of hyoscine and morphine are depressant are scarcely relevant. It is apparent that since motion sickness is not amenable to therapy in all cases it is quite possible there may be cases in which cortical factors are of decisive importance.

Of all the drugs that have been investigated so far only those of the atropine series are of consistently demonstrated value in the prevention of motion sickness. Of these, hyoscine is the most promising one because of its high degree of effectiveness and relative freedom from undesirable side effects. The dose of hyoscine hydrobromide ordinarily employed is 0.65 to 0.75 mg. repeated not more often than once in six hours. The dose of atropine ordinarily employed is 1.0 mg. with the same time interval elapsing between successive doses. The onset of action of these drugs is approximately one hour.

There is not sufficient evidence of their effectiveness to warrant the use of barbiturates, vitamins or central nervous system stimulants in motion sickness.

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Quantitative Estimation of the Albumin and Gamma Globulin in Normal and Pathologic Cerebrospinal Fluid by Immunochemical Methods*

ELVIN A. KABAT, PH.D., MURRAY GLUSMAN, M.D. and VESTA KNAUB
New York, New York

BECAUSE of the low protein content of cerebrospinal fluid, the usual chemical methods of fractionation used to measure albumin and globulin in serum are not applicable. Detection of increases in the globulin in cerebrospinal fluid is generally carried out by procedures such as the colloidal gold test^{1,2} which does not provide a direct measure of the gamma globulin but depends on the relative proportions of albumin to gamma globulin.³ Sensitivity of the gold sol used in different laboratories varies greatly and unless the test is carried out by the improved techniques of Lange⁴ it is of value chiefly in diagnosis of paresis. Whereas electrophoretic studies of cerebrospinal fluid³ have demonstrated that much of the cerebrospinal fluid protein was derived from the plasma and have provided a direct quantitative measure of the various proteins present, the large quantities of cerebrospinal fluid needed for examination precluded electrophoretic analysis as a routine diagnostic procedure.

The methods of quantitative immunochemistry appear ideally suited for the estimation of such small amounts of protein. Heidelberger and Kendall⁵ first used the quantitative precipitin method for the estimation of small quantities of specific

polysaccharides and subsequently Goettsch and Kendall⁶ applied the procedure to the estimation of albumin and globulin in serum. In subsequent studies the technic was applied to pathologic sera, lymph, ascitic fluid, edema fluid^{7,8} and its application to cerebrospinal fluid has been suggested.⁹ Data on the amounts of Benec Jones protein in the serum of a patient with multiple myeloma¹⁰ have also been obtained immunochemically. More recently Chow¹¹ has shown that values for plasma albumin obtained by the quantitative precipitin method were in general agreement with those obtained from electrophoretic analysis. Several authors¹²⁻¹⁵ report other applications of immunochemical methods.

The method requires immunization of rabbits with relatively pure preparations of the proteins to be assayed and absorption of the sera to eliminate antibodies other than those to the desired constituent. A calibration curve is then prepared by the addition of increasing quantities of the antigen to a measured volume of antiserum, the precipitates centrifuged off, washed twice in cold saline to remove non-specific protein and analyzed for nitrogen. To assay an unknown cerebrospinal fluid an appro-

* From the Departments of Neurology and Bacteriology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York, N. Y. The work reported in this communication was supported by grants from the National Multiple Sclerosis Society and the William J. Matheson Commission.

prate dilution of the fluid is added to another portion of antiserum, the precipitate washed and analyzed and the content of antigen in the volume of diluted fluid added is read off from the calibration curve and the albumin or globulin content of the undiluted cerebrospinal fluid computed; as the method has been developed analyses and calibration curves are valid only in the region of antibody excess.¹²⁻¹⁵

Among the factors which have retarded adoption of the quantitative precipitin method for routine clinical use has been the necessity for the preparation of antigens and antisera. However, large quantities of purified plasma proteins have now become available¹⁶ and it does not seem unreasonable to expect that even specific antisera might become available commercially should the demand warrant.

The present communication outlines the use of the quantitative precipitin method for the estimation of the crystalline serum albumin and gamma globulin in human cerebrospinal fluid. The proportions of albumin and gamma globulin to the total protein have been measured in normal cerebrospinal fluid and in a variety of diseases involving the nervous system. Marked increases in the proportion of gamma globulin were found in the cerebrospinal fluid in a high proportion of cases of multiple sclerosis and in patients with neurosyphilis. In the latter disease the proportion of gamma globulin appeared to correlate generally with the activity of the disease process. In a few cerebrospinal fluids evidence was obtained for an increase in the concentration of protein other than albumin and gamma globulin.

EXPERIMENTAL METHOD

Twice crystallized human serum albumin and purified human gamma globulin prepared in the laboratories of Dr. E. J. Cohn were provided by Dr. E. Brand.

To prepare antigamma globulin and anti-human crystalline albumin groups of rabbits were injected intravenously with alum or protamine precipitated antigen four times a

week for four weeks. Each rabbit received a total of about 18 mg. of protein. Five days after the last injection 50 ml. of blood were obtained from each animal by cardiac puncture. Animals were then given similar additional series of injections and bled in the same manner. The serum was separated from the blood by centrifugation in the cold. Stock solutions containing 1 mg. of antigen per ml. were prepared in saline. A drop of toluene was added as a preservative. The nitrogen content of the solutions was determined by the Markham micro-Kjeldahl method.¹⁷

A rough estimate of the antibody content of the sera was made by the addition of successive, small portions of antigen to 0.5 ml. of serum and centrifuging the precipitate formed after each addition, until no further precipitation occurred. The combined precipitates were then washed twice with cold saline and analyzed for nitrogen. Based on such preliminary analyses several antisera of about the same potency were pooled. It was found necessary to absorb the anti-globulin pools with albumin and the anti-albumin pools with globulin. For example, an antiglobulin pool of two bleedings each from two rabbits required three additions of 0.30 mg. albumin N for complete absorption. After absorption saline was added to dilute the serum to a concentration of about 100 to 150 μ g. of antibody N per ml. and merthiolate added to a final concentration of 1:10,000.

A calibration curve was prepared by the addition of increasing quantities, as for example, 3, 6, 9, 12, 15, 18, 21 μ g. N of the stock solution of antigen to a measured amount of serum, usually 1 ml. in a constant total volume of 3 ml. Each point is set up in duplicate. Two additional tubes containing only serum serve as a control. After one hour in a water bath at 37°C. and forty-eight hours in the refrigerator the precipitates are centrifuged off in a refrigerated centrifuge and washed twice with 3.0 ml. of chilled saline.⁵⁻⁸ The precipitate is then carefully dissolved in M/2 NaOH and transferred quantitatively to micro-Kjeldahl flasks and analyzed for nitrogen by the Markham micro-Kjeldahl method.¹⁷ The total N in the washed precipitate is plotted against the quantity of antigen added.

The serum supernatants from each point are combined and tested for antibody and antigen. Two ml. of supernatant are pipetted into each of two tubes. To one tube 0.15 ml. of antiserum is

added and to the other approximately 3 μ g. of antigen N is added. The tubes are placed at 37°C. for two hours and in the refrigerator overnight, then centrifuged and read. If a precipitate is obtained with antigen, the supernatant contained an excess of antibody; if precipitation occurs on addition of antibody, an excess of antigen is present. The calibration curve is valid only in the region in which antibody is in excess.

Before attempting to assay the albumin and gamma globulin of a spinal fluid it is necessary to know its total protein content so that a dilution may be selected which will give an amount of precipitate falling on the calibration curve. The total protein content is measured turbidimetrically after precipitation with sulfosalicylic acid. For spinal fluid with a total protein of 35 mg per 100 ml., 1 ml. portions may be used for the globulin determination and 1 ml. of a 1:3 dilution for the estimation of albumin. With cerebrospinal fluids of higher protein content proportionately higher, dilutions are chosen. The supernatants from each determination are also tested with antigen and antiserum to verify the presence of excess antibody. Should excess antigen be found, the analysis must be repeated with a higher dilution of cerebrospinal fluid. When some familiarity with the method has been acquired, dilutions which will regularly fall on the calibration curve may be selected without difficulty. With each set of analyses, it is advisable to check one point on the calibration curve for albumin and for globulin.

As carried out the amounts of nitrogen in the precipitates vary from 30 to 150 μ g. This range is intermediate between that ordinarily employed for quantitative precipitin assays⁵⁻⁸ and the micro method developed by Heidelberger and MacPherson.¹⁸ In the latter method, tubes are allowed to remain in the refrigerator for one week. For these studies forty-eight hours was the period of time selected for the preparation of calibration curves and for analysis of unknowns since the method would be of little clinical interest if results required a longer interval. It was noted in comparative experiments that slightly larger amounts of precipitate were found if tubes were left for a week. Since the total antibody content was of no consequence in this work, the uniform use of forty-eight hours for standards and unknowns did not in any way reduce the precision of the results.¹⁶ Validity of the method was checked by the addition of

known quantities of albumin or gamma globulin to cerebrospinal fluid and determining the recovery.

RESULTS

Table 1 summarizes data on the total protein, albumin and gamma globulin in the cerebrospinal fluid of ten healthy medical students and twenty-two patients at the Neurological Institute, admitted for various complaints, who had essentially normal spinal fluid proteins and in whom there was no reason to suspect any abnormalities in the spinal fluid protein. Among the healthy medical students, total protein ranged from 25 to 38 mg. per 100 ml., albumin from 11 to 19 and gamma globulin from 1.7 to 3.8 mg. per 100 ml. In the series of patients with presumed normal cerebrospinal fluids, total protein varied from 19 to 54, albumin from 7.6 to 29 and gamma globulin from 1.8 to 6.3 mg. per 100 ml. In the entire group of fluids the albumin to gamma globulin ratios varied from 3.8 to 8.8; the percentages of albumin to total protein and of gamma globulin to total protein from 38 to 62 and from 5 to 13. The crystalline albumin and gamma globulin accounted for from 43 to 75 per cent of the total cerebrospinal fluid protein.

The means and standard deviations¹⁹ for the data in Table 1 were as follows:

	Albumin		Gamma Globulin	
	Mean mg./100 ml.	Standard Deviation	Mean mg./100 ml.	Standard Deviation
Normals.....	15.9	2.5	2.7	0.65
Patients with proteins of 19-39 mg./100 ml. . .	14.2	4.0	3.0	0.71
Patients with proteins of 40-54 mg./100 ml. . .	22.1	3.8	4.5	1.0
All fluids in table.	17.2	4.9	3.4	1.1

It is evident that the group of patients with proteins of 19 to 39 mg. per 100 ml. fall into the same range as the ten normal

fluids; the fluids with proteins of 40 to 54 show somewhat elevated values for albumin and globulin as would be expected.

By reference to these values for the means and standard deviations the significance of the values for cerebrospinal fluid albumin

the mean by two standard deviations is about 21:1, for two and five-tenths standard deviations about 200 to 1, and for three standard deviations about 369:1.¹⁹

Table II summarizes data on the albumin and gamma globulin levels of sixteen

TABLE I
ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF HEALTHY INDIVIDUALS AND OF PATIENTS WITH PRESUMED NORMAL SPINAL FLUID PROTEIN
RESULTS OF IMMUNOCHEMICAL DETERMINATIONS

Case No.	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin/Gamma Globulin	Albumin/Total Protein	Gamma Globulin/Total Protein	Albumin + Gamma Globulin/Total Protein	Diagnoses
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.		%	%	%	
1	25	11	2.2	13	5.0	44	9	53	Healthy medical student
2	31	15	2.6	18	5.8	48	8	56	Healthy medical student
3	32	17	2.8	20	6.1	53	9	62	Healthy medical student
4	32	15	1.7	17	8.8	48	5	53	Healthy medical student
5	32	15	2.7	18	5.6	47	8	55	Healthy medical student
6	33	15	2.8	18	5.4	45	8	53	Healthy medical student
7	36	19	3.8	23	5.0	53	11	64	Healthy medical student
8	37	14	2.0	16	7.0	38	5	43	Healthy medical student
9	38	19	2.6	22	7.3	50	7	57	Healthy medical student
10	38	19	3.8	23	5.0	50	10	60	Healthy medical student

Presumed Normal Cerebrospinal Fluid

834566	19	7.4	1.8	9.2	4.1	39	10	49	Cerebral atrophy, cerebral arteriosclerosis, old cerebrovascular accident
866302	20	7.6	1.9	9.5	4.0	38	10	48	Psychoneurosis, conversion hysteria
809111	25	11	2.9	14	3.8	44	12	56	Myasthenia gravis
855976	27	13	2.4	15	5.4	48	9	57	Idiopathic epilepsy
854856	31	14	2.8	17	5.0	45	9	54	Depressive reaction, old fractured skull; mild bilateral cerebral atrophy probably post-traumatic, compression fracture of eighth vertebra post-traumatic
862560	31	15	3.0	18	5.0	48	10	58	Mixed psychoneurosis
844943	31	16	4.1	20	3.9	51	13	64	Acute myasthenia gravis, cortical atrophy, hypertrophied thymus
854637	35	15	3.1	18	4.8	43	9	52	Paralysis of right common perineal nerve, probably traumatic
839702	36	15	3.9	19	3.8	42	11	53	Facial tic, cause undetermined; moderate bilateral cerebral atrophy (more on left)
847411	36	17	3.8	21	4.5	47	11	58	Hypertensive vascular disease, generalized arteriosclerosis, deafness bilateral, cause undetermined
859436	36	16	2.9	19	5.5	45	8	53	Angiospasm; hypertensive cardiovascular disease; cerebrovascular accident, mild
855663	39	23	3.6	27	6.4	59	9	68	Psychoneurosis
850288	40	19	3.6	23	5.3	48	9	57	Syncopae, cause undetermined
846347	41	17	3.6	21	4.7	41	9	50	Psychoneurosis, anxiety state; osteoarthritis, carotid sinus syncope?
809649	44	19	4.4	23	4.3	43	10	53	Cerebral atrophy, left, post-traumatic
824809	45	20	5.1	25	4.0	45	11	56	Convulsive disorder, grand mal seizures, secondary optic atrophy
853015	45	22	3.9	26	5.7	49	9	58	Right brachial neuritis, result of old right radical mastectomy; metastatic carcinoma right scapula
850089	47	24	3.3	27	7.2	51	7	58	Torticollis; spastic osteoarthritis cervical spine
852155	47	24	4.5	29	5.3	51	10	61	Sciatic syndrome, cause undetermined
859144	47	29	6.3	35	4.6	62	13	75	Headaches, histamine sensitivity?, psychogenic?
849821	48	19	4.4	23	4.3	40	9	49	Right hemiparesis, birth injury; myositis ossificans
823611	54	28	6.1	34	4.6	52	11	63	Psychoneurosis

and globulin in various neurologic diseases may be evaluated. The probability of significance for values which deviate from patients with neurosyphilis. Data on colloidal gold and Wassermann tests on the cerebrospinal fluid sample analyzed are

also given. Of the seventeen cerebrospinal fluids, ten had total proteins within the range accepted as normal in Table I and in all of these instances the albumin was within the normal range; of the remaining seven fluids with high total proteins, one

increase being two and two-tenths standard deviations from the mean for fluids in that range of total spinal fluid protein. The gamma globulin values of these sixteen fluids varied from 5.6 to 116 mg. per 100 ml. and the percentage of gamma globulin to

TABLE II
ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH NEUROSYPHILIS

Case No	Total Protein	Al- bumin	Gam- ma Glo- bulin	Al- bumin + Gam- ma Glo- bulin	Al- bumin Gam- ma Glo- bulin	Al- bumin Total Pro- tein	Gam- ma Glo- bulin Total Pro- tein	Al- bumin + Gam- ma Glo- bulin Total Pro- tein	Colloidal Gold	Spinal Fluid Wassermann	Activity of Disease
	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.		%	%	%			
808655	36	15	5.6	21	2.7	42	16	58	Negative	Negative	Cerebrospinal syphilis, asymptomatic; improved following penicillin and fever eight months previous
832208	44	23	7.5	31	3.1	52	17	69	Negative	++ (2 ml.)	Meningovascular syphilis; definitely improved following penicillin and fever ten months previous
848591	41	19	6.7	26	2.8	46	16	62	Negative	Negative*	Neurosyphilis manifested by bilateral optic atrophy; activity questionable
560946	87	34	3.2	37	11	39	4	43	4333221100	++++ (0.2 ml.)	Meningovascular syphilis, some improvement
856884	45	14	26	40	0.5	31	58	89	1122211000	++++ (0.2 ml.)	Active meningovascular syphilis with involvement of optic nerves
857091	74	40	27	67	1.5	54	36	90	1112211000	++++ (0.2 ml.)	Central nervous system lues, vascular type; moderately active, progressing at time of admission
866326	35	19	8.1	27	2.3	54	23	77	Negative	++++ (1.0 ml.)	Central nervous system lues, tabes dorsalis, Charcot spine, progression questionable at time of admission
859593	46	22	11	33	2.0	48	24	72	Negative	Negative	Taboparesis, questionably active, recent improvement following penicillin
764893	65	35	17	52	2.0	54	26	80	1122211000	++++ (2 ml.)	Juvenile taboparesis, active
871521	68	34	28	62	1.2	50	41	91	2223332110	++++ (1 ml.)	Taboparesis active, recent marked improvement following penicillin
862203	78	55	21	76	2.6	70	27	97	Negative	Negative	Central nervous system lues, tabetic, activity questionable, hypertensive cardiovascular disease
853703	68	33	20	53	1.7	49	29	78	Negative	++++ (2 ml.)	Central nervous system lues clinical manifestations slight, Ménière's syndrome, diabetes mellitus
	42	24	10.6	35	2.3	57	25	82	Negative	++++ (2 ml.)	(Sample twenty-four days later after 9,000,000 units penicillin)
851022	42	15	17	32	0.9	36	40	76	2222100000	++++ (2 ml.)	Active general paresis; some improvement following penicillin and fever
863603	48	16	14	30	1.1	33	29	62	Negative	++++ (1 ml.)	Active general paresis; received penicillin five months previous
857499	49	15	33	48	0.5	31	67	98	3222110000	++++ (0.2 ml.)	Early, moderately active general paresis
852151	141	24	116	140	0.2	17	82	99	Negative	++++ (0.2 ml.)	Active general paresis

* Serum Kline + + + +.

showed a normal albumin and the remaining six showed somewhat elevated albumins. The most striking changes were found in the amounts of gamma globulin. Sixteen of the seventeen fluids showed a striking increase in the gamma globulin level, the smallest

total protein from 16 to 82. It is noteworthy that in this group of sixteen the three lowest values for gamma globulin were in the patients who had shown a good response to therapy eight to ten months previously and were improving, had become asymp-

tomatic, or had a process of questionable activity. In this respect determination of cerebrospinal fluid gamma globulin offers promise as an indicator of the effectiveness of antiluetic therapy. All sixteen fluids showed albumin to gamma globulin ratios

in that the sum of the albumin and gamma globulin accounted for only 37 of the 87 mg. of protein in the fluid. This unusually low recovery, together with the finding of a paretic colloidal gold curve, indicates the presence of a considerable amount of a

TABLE III
ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS
WITH DISSEMINATED ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS

Case No.	Total Protein	Albu- min	Gamma Globu- lin	Albu- min + Gamma Globu- lin	Albu- min Gamma Globu- lin	Albu- min Total Protein	Gamma Globu- lin Total Protein	Albu- min + Gamma Globu- lin Total Protein	Colloidal Gnld	Diagnoses and Activity of Disease
	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.		%	%	%		
740229	17	6.5	1.3	7.8	5.0	38	8	46	Negative	Acute disseminated encephalomyelitis due to pertussis vaccine, beginning recovery from acute episode
866335	23	8.8	2.1	10.9	4.2	38	9	47	Negative	Acute disseminated encephalomyeloradiculitis, rapid onset, marked activity, some improvement in hospital
848899	51	22	3.6	26	6.2	44	7	51	Negative	Multiple sclerosis, very slowly progressive, seventeen years' duration
853494	26	14	3.1	17	4.5	54	12	66	Negative*	Multiple sclerosis, mild to moderate severity, moderately progressive, three years' duration
868189	35	19	3.1	22	6.1	54	9	63	Negative	Multiple sclerosis, moderately severe, moderately progressive, six years' duration
817816	32	8.6 9.0	4.5 3.8	13.1 12.8	1.9 2.4	27 28	14 12	41 40	Negative	{ Multiple sclerosis, slight improvement in moderately active case
863801	39	19	5.6	25	3.4	49	14	63		
864977	26	12	3.8	16	3.2	46	15	61	Negative*	Multiple sclerosis, moderately severe, moderately progressive, six years' duration
864707	27	11	4.1	15	2.7	41	15	55	Negative	Multiple sclerosis, mild, slight activity, four years' duration
835706	39	20	6.0	26	3.3	51	15	66	Negative	Multiple sclerosis, fairly early, mild, slight improvement
859087	48	21	8.5	29	2.5	44	18	62	Negative	Multiple sclerosis, improved following exacerbation
864021	37	16	7.9	24	2.0	43	21	64	*	Multiple sclerosis, mild severity, mild exacerbation, seven years' duration
915 (Albany)†	48	25	12	37	2.1	52	25	77	Negative	* Multiple sclerosis
774971	48	22	15	37	1.5	45	31	76		
860909	34	12	11	23	1.1	35	32	68	1122211100	Multiple sclerosis, moderate severity, slowly progressive, four years' duration
857874	38	15	13	28	1.2	40	34	74	1122100000*	Multiple sclerosis, mild; moderate activity, progressive; two years' duration
										Multiple sclerosis, moderate severity, moderately active, two and one-half years' duration

* Typical paretic colloidal gold curves were found in these fluids by Drs. C. Lange and A. H. Harris by their more delicate procedure.⁴
† Fluid supplied by Drs. Lange and Harris.

considerably lower than any of the fluids in Table 1. Since ten of the seventeen fluids were negative in the usual colloidal gold test which depends upon the albumin as well as the gamma globulin level,³ the present method would appear to be more sensitive.
The seventeenth fluid (No. 560,946) showed a normal gamma globulin and a slightly elevated albumin, but was unusual

protein other than albumin and gamma globulin. From the low gamma globulin value it is very unlikely that the gamma globulin could be responsible for the paretic colloidal gold curve.¹⁻³
Table III summarizes data obtained in two cases of disseminated encephalomyelitis and fourteen cases of multiple sclerosis. The patients with disseminated encephalomyelitis showed essentially normal values for

spinal fluid albumin, gamma globulin and total protein. All of the fourteen patients with multiple sclerosis showed total protein levels within the range accepted as normal in Table 1. Of these, all but one showed essentially normal albumins; the exception

gamma globulin values three or more standard deviations from their corresponding means. Of the eleven fluids tested, all but the two fluids with the highest gamma globulin levels showed negative colloidal gold tests as carried out in the usual manner.

TABLE IV

ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH VARIOUS NEUROLOGIC DISEASES

Case No	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin/Gamma Globulin	Albumin/Total Protein	Gamma Globulin/Total Protein	Albumin + Gamma Globulin/Total Protein	Diagnoses
	mg/100 ml	mg/100 ml	mg/100 ml	mg/100 ml		%	%	%	
852380	36	14	3.3	17	4.2	39	9	18	Amiotrophic lateral sclerosis
847446	38	19	3.1	22	6.1	50	8	58	Amiotrophic lateral sclerosis
851254	70	30	5.3	35	5.7	43	8	51	Amiotrophic lateral sclerosis
857377	33	18	2.9	21	6.2	55	9	64	Pernicious anemia, subacute combined degeneration
854387	32	14	12	26	1.2	44	38	82	Degenerative cord disease
850392	39	26	5.3	31	4.9	67	14	81	Degenerative cord disease
856878	64	33	7.0	40	4.8	52	11	63	Herniated nucleus pulposus
853265	100	56	15	71	3.7	56	15	71	Herniated nucleus pulposus
846548	106	61	17	78	3.7	58	16	74	Acute anterior poliomyelitis
854040	400	172	61	233	2.8	43	15	58	Acute anterior poliomyelitis
849428	55	28	6.8	35	4.0	51	12	63	Myoclonus epilepsy
845614	35	16	3.1	19	5.1	46	9	55	Paralysis agitans, arteriosclerotic
854591	53	35	5.0	40	7.0	66	9	75	Paralysis agitans, generalized arteriosclerosis, arteriosclerotic heart disease, diabetes mellitus
862302	47	27	5.5	33	4.9	57	12	69	Presenile psychosis, cerebral arteriosclerosis, mastoiditis chronic
845101	63	31	5.0	36	6.2	49	8	57	Generalized and cerebral arteriosclerosis
842927	20	7.9	2.9	10.8	2.6	40	15	55	Pituitary adenoma
829778	38	19	5.1	24	3.7	50	13	63	Pituitary chromophobe adenoma, bilateral cervical ribs
844137	42	20	3.9	24	5.1	48	9	57	Oligodendroglioma (right lateral ventricle) verified by operation
	39	18	3.2	21	5.6	46	8	54	Oligodendroglioma (sample taken fourteen days after first)
844971	258	114	50	164	2.3	44	19	63	Left frontal lobe abscess (communicating with the ventricular system) demonstrated by operation, basal meningitis organism undetermined
848484	108	35	9.7	45	3.6	32	9	41	Basilar and spinal leptomeningitis chronic, secondary hydrocephalus probably result of suppurative leptomeningitis, organism undetermined
759207	96	43	6.9	50	6.2	45	7	52	Chronic encephalitis
841765	800	410	244	653	1.7	51	31	82	Cryptococcus hominis neoformans, leptomeningitis with focal encephalitis (autopsied)
	980	480	294	774	1.6	49	30	79	
768060	420	220	46	268	4.8	53	13	66	Cryptococcus hominis neoformans meningitis
863998	126	65	13	78	5.0	52	10	62	Guillain-Barré syndrome
838446	164	101	35	136	2.9	62	21	83	Guillain-Barré syndrome
852435	165	97	22	119	4.4	59	13	72	Guillain-Barré syndrome
	80	45	10	55	4.5	56	13	69	Guillain-Barré syndrome (sample of fluid seven days later)
862444	296	141	38	179	3.7	48	13	61	Guillain-Barré syndrome
853710	330	191	56	247	3.4	58	17	75	Guillain-Barré syndrome

(No. 817,816) was somewhat low in albumin. With respect to their content of gamma globulin, three patients had levels within one standard deviation from the mean for their range of total protein, the values in three others were between one and two standard deviations higher than the mean, and the remaining eight had

However, Drs. Carl Lange and A. H. Harris, at Albany, assayed five of the fluids by their more sensitive procedure⁴ and the fluids were found to give definite parietic curves. Eleven of the fourteen fluids had albumin to gamma globulin ratios below the lowest of the fluids in Table 1 and the percentage of gamma globulin was higher

in ten of the fluids than the highest corresponding value in Table I. Fluid No. 817,816 was unusual in that the albumin and gamma globulin accounted for only 13 to 14 of the 32 mg. of protein, again suggesting the presence of increased quantities of some other protein. (No. 560,946, Table II.) The two sets of values represent repeated determinations on the same sample of fluid and provide an indication of the reproducibility of the method. Data on the activity of multiple sclerosis are included, but no correlation between the phase of the disease and the spinal fluid gamma globulin is as yet apparent.

Data on the spinal fluid proteins in a variety of other neurologic disorders are given in Table IV. Two of three patients with amyotrophic lateral sclerosis showed normal total protein and albumin and gamma globulin values; the third had a high total protein but the proportions of albumin and gamma globulin were normal. Essentially normal values were also found in one patient with pernicious anemia with subacute combined degeneration, one with oligodendroglioma, two with pituitary adenomas and in two of four patients with arteriosclerosis. Of the remaining two patients one showed a high total protein (845,101) and the other a high albumin (854,591). One of two patients with degenerative cord disease showed a marked increase and the other a slight rise in gamma globulin. Two subjects with herniated nucleus pulposus showed an increase in total protein and the albumin and gamma globulin were also correspondingly increased. Similar findings were also noted in two patients with poliomyelitis. The remaining cases comprise those with fluids with very high total proteins. In these instances there is, as previously pointed out from electrophoretic data,³ chiefly an increase in all of the spinal fluid proteins. However, one of two patients with meningitis due to *Cryptococcus hominis*, one with cerebral abscess and two of six patients with Guillain-Barré syndrome showed increases in the proportion of gamma globulin.

COMMENTS

The immunochemical methods employed in these studies provide a direct measure of the quantities of albumin and gamma globulin in cerebrospinal fluid on a weight basis. When combined with determinations of the total protein of the cerebrospinal fluid, the three values enable differences in proportions of these constituents to be readily established. In addition, an indication of changes in proteins other than albumin and gamma globulin may be obtained by difference. Results, in general, confirm and extend those previously obtained by electrophoresis.³ Although the same fluids were not examined by both methods, the values for albumin and gamma globulin for presumed normals³ calculated from electrophoretic patterns are in general agreement with the values reported above. While the quantities of fluid required for electrophoretic analysis are so large as to preclude its routine diagnostic use even when the Tiselius apparatus is available, the present method requires at most but 6 or 7 ml. of cerebrospinal fluid for duplicate albumin and gamma globulin determinations and estimation of total protein. Among other advantages are that a number of analyses may be carried out at the same time and that specialized apparatus is not required. If a refrigerated centrifuge is not available, a small centrifuge placed in an icebox or cold room is adequate. As described, about three days is the minimum time between receipt of the sample and completion of the analyses. The method, unlike the salt-fractionation procedures, is not affected by the total protein concentration and is specific for the constituents to be measured. The absorbed antialbumin and antigamma globulin sera did not react with fibrinogen and, since supernatants from the calibration curves and the spinal fluids did not show a zone in which both antibody and antigen were present, it is reasonable to infer that each absorbed antiserum contained antibody only to the antigen which it was desired to estimate.^{8,12,13,14,15,20}

In addition, the same values were obtained when a given spinal fluid was analyzed with several calibrated antisera. Further evidence that the absorbed antisera were specific was obtained by the technic of Oudin²¹ in which human serum was layered over agar gels containing the respective absorbed antisera. As diffusion into the gel took place only a single band of specific precipitate was observed with each antiserum corresponding to that obtained by layering the antigen used in preparing the antiserum over a similar agar gel. No band was observed with the heterologous antigen. Although it is more involved than the colloidal gold test, it provides values which are independent of the other proteins present.

The results indicate that the method is of greatest value with those cerebrospinal fluids with normal or somewhat elevated total protein levels in that it provides information about changes in the relative proportions of the constituents. With fluids with very high total protein (above 200), it has thus far provided very little additional information of clinical significance.

It is evident that definite increases in the absolute amount and in the percentage of gamma globulin occurred in the cerebrospinal fluid of those with neurosyphilis (Table II) and in a large proportion of patients with multiple sclerosis. (Table III.) Patients with active neurosyphilis showed extraordinarily elevated gamma globulins while those individuals who had been treated successfully or who did not show evidence of activity had gamma globulins which were much lower and presumably were returning to normal. It would appear that estimation of spinal fluid gamma globulin may be of value as a guide in evaluating antiluetic therapy.

Findings of a significantly increased gamma globulin in eight of fourteen patients with multiple sclerosis and of an increase in the percentage of gamma globulin to total protein in ten of these patients strongly suggests the usefulness of this test in helping to establish the

diagnosis of multiple sclerosis, a diagnosis which is not infrequently quite difficult to make with certainty. Present data are not sufficient to establish the relation between the stage of the disease and the gamma globulin level. Further studies are contemplated in which a group of patients will be followed over a considerable period to elucidate this point. It is perhaps significant that the two patients with acute disseminated encephalomyelitis showed normal albumin and globulin values.

SUMMARY

1. An immunochemical method for the estimation of albumin and gamma globulin in cerebrospinal fluid is outlined.

2. Normal values for albumin and gamma globulin are presented.

3. In fifteen of sixteen cases of neurosyphilis, increases in gamma globulin were found. The highest values were found in those patients with active neurosyphilis and the lowest in patients who had shown a favorable response to therapy.

4. Eight of fourteen patients with multiple sclerosis showed an increased spinal fluid gamma globulin.

5. Data on cerebrospinal fluid albumin and gamma globulin in a variety of other diseases are presented.

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Serum Proteins in Syphilis*

Electrophoretic Study

EARL P. BENDITT, M.D. and SHELDON A. WALKER, M.D.

Chicago, Illinois

THE Tiselius method of electrophoresis¹⁶ offers a tool with which to investigate certain properties of colloidal mixtures including the serum proteins. The method has been used to study serum proteins in many diseases and interesting changes have been found.^{6,8,15} The physiologic and pathologic significance of these findings remains in large part to be worked out.

It has been stated that in syphilis there are changes in the electrophoretic pattern of the serum proteins which are "characteristic and statistically significant."³ These changes consisted in an "increase in all of the electrophoretic globulin fractions." Others¹¹ demonstrated the changes in this disease to be of a more limited nature and to consist of a decrease in albumin and an increase in gamma globulin. Similar alterations were found in biologic false-positive sera.

The present studies were undertaken in order to (1) re-examine the electrophoretic pattern changes in syphilis, (2) to correlate the pattern alterations with the stage of the disease, the effects of treatment and other possible influencing factors and (3) further evaluate the use of electrophoresis as an aid in the serologic diagnosis of syphilis.

METHODS AND MATERIALS

Patients in this study were derived mainly from the clientele of the University of Chicago Clinics. Those with primary disease were from the Chicago Intensive Treatment Center. An attempt was made to obtain serum from patients who had (1) a definite diagnosis of syphilis

on evidence other than serologic tests, (2) patients in all stages of the disease, and (3) patients with and patients without previous treatment. A small group of patients was studied in whom the serologic tests were positive, but in whom there was some reason to doubt the presence of syphilis. They were followed until it was decided definitely that there was no syphilis present. Control sera were obtained from healthy men and women of the Clinics staff. Only those without recent acute infections were used.

Blood was drawn in the morning before breakfast. It was allowed to clot at room temperature for several hours and the serum separated by centrifugation. Sera were stored in the frozen state at -15°C . We have tested the acute effects of freezing and thawing upon both human and rat sera and have found no alteration beyond the limits of experimental error.

Four milliliters of serum were dialysed against 2 liters of buffer for a minimum of forty-eight hours at 4°C . The buffer was composed of 0.100 moles of sodium diethylbarbiturate, and 0.020 moles of diethylbarbituric acid per liter of solution.⁹ The ionic strength of this buffer is 0.1 and the pH 8.6. At the end of dialysis the serum was diluted to 12.0 milliliters by the addition of the requisite amount of buffer.

Electrophoresis was carried out in a double section Tiselius cell.¹⁶ The apparatus used varied slightly from the usual design in that the schlieren and camera lenses had a focal length of 38 cm. The optical system was otherwise of the type described by Philpot.¹² The potential gradient was approximately 8 volts per cm. and the bath temperature 1°C . Runs were of seventy to eighty-minutes' duration. It has been shown that adequate separation for measurement can be achieved after sixty minutes at a potential gradient of 6.5 volts per cm.⁴

* From the Department of Pathology and the Section of Dermatology, Department of Medicine, University of Chicago, Chicago, Ill.

Patterns were enlarged five diameters and traced. The individual components were separated by vertical lines drawn from the minima of the curves to the baseline. Area measurements were made with a planimeter. Both ascending and descending limb patterns from each analysis

delineation of the components and their measurement with the planimeter. Duplicate tracings and measurements were made on thirteen individual patterns by two observers. The coefficient of variation for the total pattern area was found to be ± 1.71 per cent. Computed on the basis

TABLE I
ELECTROPHORETIC DATA FOR NORMAL HUMAN SERA

Case No.	Sex	Age	% Composition					Component Concentration Gm. %					
			Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Normal Males													
N1	M	24	60.6	5.4	9.4	14.7	9.8	4.16	0.37	0.65	1.01	0.67	6.86
N2	M	31	55.7	4.6	8.7	18.4	12.7	4.16	0.35	0.65	1.37	0.95	7.47
N3	M	22	56.3	4.5	9.8	16.8	12.6	3.96	0.32	0.69	1.18	0.89	7.04
N4	M	22	57.5	5.7	10.2	18.3	8.3	4.07	0.40	0.72	1.29	0.59	7.07
N5	M	17	57.2	4.6	8.9	14.3	15.0	3.96	0.32	0.62	0.99	1.04	6.93
Mean	57.5	5.0	9.4	16.5	11.7	4.06	0.35	0.67	1.17	0.83	7.07
S.D.	1.90	0.55	0.80	1.94	2.64	0.100	0.034	0.039	0.168	0.19	0.237
Normal Females													
N6	F	24	61.3	3.7	9.1	13.1	12.8	4.45	0.27	0.66	0.95	0.93	7.26
N7	F	33	54.4	5.5	10.6	17.5	12.0	3.36	0.34	0.65	1.08	0.74	6.17
N8	F	36	60.1	4.3	8.3	13.5	13.9	3.95	0.28	0.54	0.89	0.91	6.57
N9	F	21	52.7	4.1	10.7	14.5	17.9	4.04	0.31	0.82	1.11	1.37	7.65
N10	F	20	59.6	4.2	7.7	14.0	14.6	4.28	0.30	0.55	1.01	1.05	7.19
N11	F	23	60.6	5.7	7.9	13.7	12.0	3.85	0.36	0.50	0.87	0.76	6.34
N12	F	21	60.3	4.6	8.6	14.0	12.5	3.75	0.29	0.53	0.87	0.78	6.22
Mean	58.4	4.6	9.0	14.3	13.7	3.95	0.31	0.61	0.97	0.93	6.77
S.D.	3.41	0.74	1.23	1.47	2.10	0.357	0.032	0.112	0.101	0.222	0.588
Combined Normals													
Mean	58.0	4.7	9.2	15.2	12.8	4.00	0.32	0.63	1.05	0.89	6.90
S.D.	2.81	0.67	1.00	1.95	2.45	0.276	0.039	0.091	0.162	0.207	0.483

were measured. The values for each component were averaged except in the case of beta globulin. Because of the descending limb beta boundary anomaly, only the ascending area was used for this component.

An estimate of the error in the method was made as follows: Assuming that with a given electrophoresis apparatus the same sample of serum will produce the same pattern each time it is separated under the same conditions, then the error in the determination lies in the reproducibility of the enlarged pattern tracings, the

of serum protein concentration (for an average value of 7.0 Gm. per cent) the error is ± 0.12 Gm. per cent. Errors in the individual components were all of a similar order of magnitude and varied between ± 0.04 and ± 0.08 Gm. per cent.

Protein concentration was estimated by determining the protein nitrogen of the serum by micro-Kjeldahl and using the factor 6.25:

Serologic tests were done in most instances on the same serum used for electrophoresis; in the remainder the tests were done on sera drawn

within a few days of that used for fractionation. Multiple serologic examinations were done on all patients. Tests were run either in the laboratory of the Chicago Intensive Treatment Center or the Serology Laboratory of the University of Chicago Clinics. Kahn tests were done on all sera; the Wassermann test was done on all except those who had primary lesions. The Treponema

pallidum was demonstrated in all of the primary lesions by dark field examination.

EXPERIMENTAL OBSERVATIONS

The essential clinical and electrophoretic data for normal controls, untreated and treated syphilitic patients, respectively, are

TABLE II
CLINICAL AND ELECTROPHORETIC DATA FOR UNTREATED SYPHILITIC PATIENTS

Case No.	Sex	Age	Duration of Disease	Clinical Signs	Serology	Complications	% Composition					Component Concentration Gm. %					
							Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Primary Syphilitics																	
P1	F	19	6 days	+	Pos.	0	50.1	5.0	9.8	16.2	18.9	3.44	0.34	0.67	1.11	1.29	6.86
P2	F	18	14 days	+	Pos.	0	43.1	5.9	11.2	12.7	27.2	3.15	0.43	0.82	0.92	1.99	7.31
P3	M	27	7 days	+	Neg.	0	59.1	3.4	8.8	14.7	14.1	4.47	0.25	0.66	1.11	1.07	7.86
P4	F	17	7 days	+	Pos.	+*	45.5	5.1	10.2	12.3	27.0	3.53	0.39	0.79	0.95	2.09	7.75
P5	F	18	?	+	Neg.	+†	46.2	5.2	9.8	15.6	23.2	3.67	0.41	0.78	1.24	1.84	7.94
Mean	48.8	4.9	10.0	14.3	22.1	3.65	0.36	0.74	1.07	1.66	7.54
S.D.	6.28	0.92	0.87	1.73	5.60	0.495	0.072	0.074	0.131	0.451	0.425
Secondary Syphilitics																	
S1	F	23	?	+	Pos.	+‡	39.4	8.5	15.6	17.3	19.2	2.78	0.60	1.10	1.22	1.35	7.05
S2	F	22	4 mo.	+	Pos.	0	48.7	6.4	10.3	14.4	20.2	3.54	0.47	0.75	1.04	1.47	7.26
S3	F	19	5 mo.	+	Pos.	0	48.6	4.5	8.8	14.5	23.6	3.70	0.34	0.66	1.10	1.80	7.61
S4	M	42	3 mo.	+	Pos.	0	42.8	7.8	14.9	16.2	18.2	2.68	0.49	0.93	1.01	1.14	6.25
S5	F	23	?	+	Pos.	0	50.2	4.4	14.1	14.9	16.4	3.55	0.31	1.00	1.05	1.16	7.07
S6	M	26	48 days	+	Pos.	0	57.1	6.4	9.5	13.3	13.7	4.15	0.47	0.69	0.97	1.00	7.28
Mean	47.8	6.3	12.2	15.1	18.6	3.40	0.45	0.86	1.07	1.32	7.09
S.D.	6.16	1.67	3.00	1.43	3.38	0.345	0.106	0.181	0.087	0.288	0.457
Tertiary Syphilitics																	
T1	M	67	25 yr.	+	Pos.	+§	49.1	6.9	11.9	13.8	18.2	3.38	0.47	0.82	0.95	1.25	6.87
T2	M	56	15 yr.	+	Pos.	0	51.8	3.6	10.7	18.9	15.0	3.63	0.25	0.75	1.32	1.05	7.00
T3	M	57	?	+	Pos.	0	50.6	4.9	9.0	16.1	19.5	3.68	0.35	0.65	1.17	1.41	7.26
T4	M	42	19 yr.	+	Pos.	0	46.6	5.0	12.6	16.2	19.7	3.39	0.36	0.92	1.18	1.44	7.29
Mean	49.5	5.0	11.0	16.2	18.1	3.52	0.36	0.78	1.16	1.29	7.10
S.D.	2.24	1.35	1.58	2.09	2.17	0.157	0.090	0.114	0.153	0.179	0.202
Congenital Syphilitic																	
C1	F	13	13 yr.	0	Pos.	0	57.6	5.4	8.3	11.8	16.9						

* Gonorrhea

† Chancroid

‡ Eleven days post partum

§ Arteriosclerosis; hypertension

found in Tables I, II and III. Electrophoretic data are presented both as percentage composition of the pattern and as concentration in Gm. per cent of the individual components. In Table IV are the data for

by others² that these are not significantly altered. The general configuration of all the patterns is not markedly different, and the descending beta globulin anomaly is present in all cases.

TABLE III
CLINICAL AND ELECTROPHORETIC DATA FOR TREATED SYPHILITIC PATIENTS

Case No.	Sex	Age	Duration of Disease	Clinical Signs	Serology	Complications	Duration of Treatment	% Composition					Component Concentration Gm. %					
								Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Secondary Syphilitics																		
ST1	F	38	1½ yr.	+	Pos.	+†	2 wk.	51.0	5.8	10.2	20.3	12.7	3.44	0.39	0.69	1.37	0.86	6.75
ST2	M	26	2 mo.	+	Pos.	0	8 days	57.7	5.5	8.9	15.2	12.7	4.52	0.43	0.70	1.19	1.00	7.84
ST3	F	23	?	+	Pos.	0	8 days	50.6	5.0	12.4	16.1	15.9	3.39	0.33	0.83	1.08	1.06	6.69
ST4	F	36	3 yr.	+	Pos.	0	1½ yr.	50.6	5.1	9.3	18.6	16.3	3.73	0.38	0.69	1.37	1.20	7.39
ST5	M	26	2 yr.	0	Neg.	0	2 yr.	59.2	4.4	8.3	15.6	12.5	4.09	0.30	0.57	1.08	0.86	6.92
Mean	53.8	5.2	9.8	17.2	14.0	3.83	0.37	0.70	1.22	1.00	7.12
S.D.	6.35	0.79	2.24	3.28	2.84	0.706	0.076	0.137	0.217	0.214	0.728
Tertiary Syphilitics																		
TT1	F	33	?	0	Pos.	0	8 mo.	54.8	4.9	10.1	17.7	12.5	3.71	0.33	0.69	1.20	0.84	6.77
TT2	M	61	5 yr.	+	Pos.	0	1 yr.	52.3	3.6	9.4	14.6	10.1	3.74	0.22	0.56	0.87	0.61	6.00
TT3	M	68	26 yr.	+	Pos.	+†	2 mo.	52.9	4.3	10.4	16.8	15.6	3.91	0.32	0.77	1.24	1.15	7.40
TT4	F	39	?	0	Pos.	0	4 yr.	58.8	3.7	9.1	15.1	13.4	4.79	0.30	0.74	1.23	1.09	8.16
TT5	F	48	13 yr.	+	Pos.	0	5 yr.	62.1	3.9	8.4	14.5	11.1	4.22	0.27	0.57	0.98	0.75	6.79
TT6	M	46	1 yr.*	+	Pos.	0	1 yr.	46.3	6.5	14.4	14.9	17.8	3.04	0.43	0.95	0.98	1.17	6.57
TT7	F	22	3 yr.	0	Pos.	0	3 yr.	56.1	5.4	10.8	12.4	15.3	3.82	0.37	0.74	0.84	1.04	6.81
TT8	F	52	30 yr.	+	Neg.	0	3 yr.	48.1	7.2	11.4	18.5	14.8	3.70	0.55	0.87	1.42	1.14	7.69
TT9	F	56	12 yr.	+	Pos.	0	1½ yr.	57.7	3.8	8.0	13.4	16.9	3.66	0.24	0.51	0.85	1.07	6.35
Mean	55.5	4.8	10.2	15.3	14.2	3.84	0.34	0.71	1.07	0.98	6.95
S.D.	5.64	1.32	1.92	1.99	2.59	0.471	0.103	0.146	0.209	0.180	0.681
Congenital Syphilitics																		
CT1	M	28	28 yr.	+	Neg.	0	16 yr.	61.5	4.2	7.8	12.5	13.9	3.96	0.27	0.50	0.81	0.90	6.45
CT2	M	7	7 yr.	+	Pos.	0	5 yr.	58.2	4.0	8.4	11.5	17.9	3.71	0.25	0.54	0.73	1.14	6.37

* Premature tertiary lesions

† Pregnancy

‡ Arteriosclerosis; hypertension

three patients with biologic false-positive sera.

Figure 1 presents eight representative serum electrophoretic patterns from controls and patients in all stages of the disease. As can be seen no new components are evident, nor are there any gross alterations in mobilities apparent. Mobilities were not computed from the data, but it has been shown

Control Sera. Determinations were made on twelve normal human sera. Five were from males and seven from females. It is evident (Table I) that the concentrations of alpha-1 and beta globulins are slightly lower in the females. The difference is of borderline significance statistically. A larger series would be necessary to define this difference. Otherwise the patterns appeared

identical in composition. The mean values for the combined normal series were used in the statistical comparisons with the various groups of pathologic sera. Differences were considered "significant" if the statistical probability of their being real

untreated group had negative serologic reactions. Both of these were cases of primary disease. One of them (P-3) had a normal electrophoretic pattern, the other (P-5) had marked changes of the characteristic type. The latter patient also had

TABLE IV
ELECTROPHORETIC DATA FOR PATIENTS WITH FALSE-POSITIVE SEROLOGY

Case No.	Sex	Age	Symptoms or Signs	SeroLOGY	Spinal Fluid	Treatment	% Composition					Component Concentration Gm. %					
							Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	T
Q3	F	42	Recent nerve deafness	Neg. to 4+ to Neg.	Neg.	0	52.58	6.50	11.29	17.66	11.98	3.72	0.46	0.80	1.25	0.85	7.07
Q4	F	23	Pregnant	3+ to Neg.		0	55.37	5.66	12.22	14.37	12.37	3.18	0.33	0.70	0.83	0.71	5.75
Q7	F	48	Neuralgia maxillary nerve	1+ to 3+ to Neg.	Neg.	(1938) 8 mo.	48.04	4.92	9.52	23.01	14.52	3.18	0.33	0.63	1.52	0.96	6.62

was greater than 95 out of 100 (i.e., P less than .05).

Untreated Syphilis. The most striking deviation from the normal in the syphilitic sera is the fall in albumin. It is apparent in the primary stage of the disease and remains in the secondary and tertiary stages. The change is evident in both the relative percentage and in the concentration.

The alpha-1 globulin deviates from the normal significantly only in secondary syphilis in which it appears elevated. The alpha-2 globulin is significantly increased in both the secondary and tertiary untreated syphilitics. Beta globulin is not significantly altered in any stage of the untreated disease. In all stages of untreated syphilis the gamma globulin is significantly elevated. Total protein concentration does not vary significantly from the normal in any stage of the disease.

Effect of Treatment. Treated secondary and tertiary syphilitics show only small deviations from the normal in their electrophoretic serum components. These differences are not statistically significant.

Serologic Reaction vs. Altered Serum Protein Fractions. Two of the patients in the

chaneroid which may have influenced the pattern.

Not all of the patients with positive serologic reactions have electrophoretic patterns which deviate significantly from the normal. This is particularly evident in the treated patients, of whom ten of the total of twelve have positive serologic reactions, but on the average there is no significant deviation from the normal in their patterns.

Congenital Syphilis. Only three sera were available for study. Two of these were from treated patients and one from an untreated patient. In none of these cases is there any marked deviation from the normal.

Positive Serologic Reaction without Syphilis. In Table IV are the data for three persons who had positive serologic reactions at the time the sera for electrophoresis were collected. These were all declared non-syphilitic on clinical evidence after a follow-up period of one year. In addition, in all patients, the Wassermann reaction eventually reverted to negative spontaneously. These patterns deviate from the normal principally in having low albumin values. Cases Q-3 and Q-4 had elevated alpha-2 globulins and case Q-7 had a markedly

elevated beta globulin. In none of these patients did the gamma globulin deviate significantly from the normal.

Other Factors. The relatively small number of patients examined from the electrophoretic standpoint precluded the possibility

similar to those observed by Neurath,¹¹ the full data for which have recently been published by G. R. Cooper and others.² They cannot be directly compared with the findings of J. A. Cooper³ because of a difference in the methods of expressing globulin

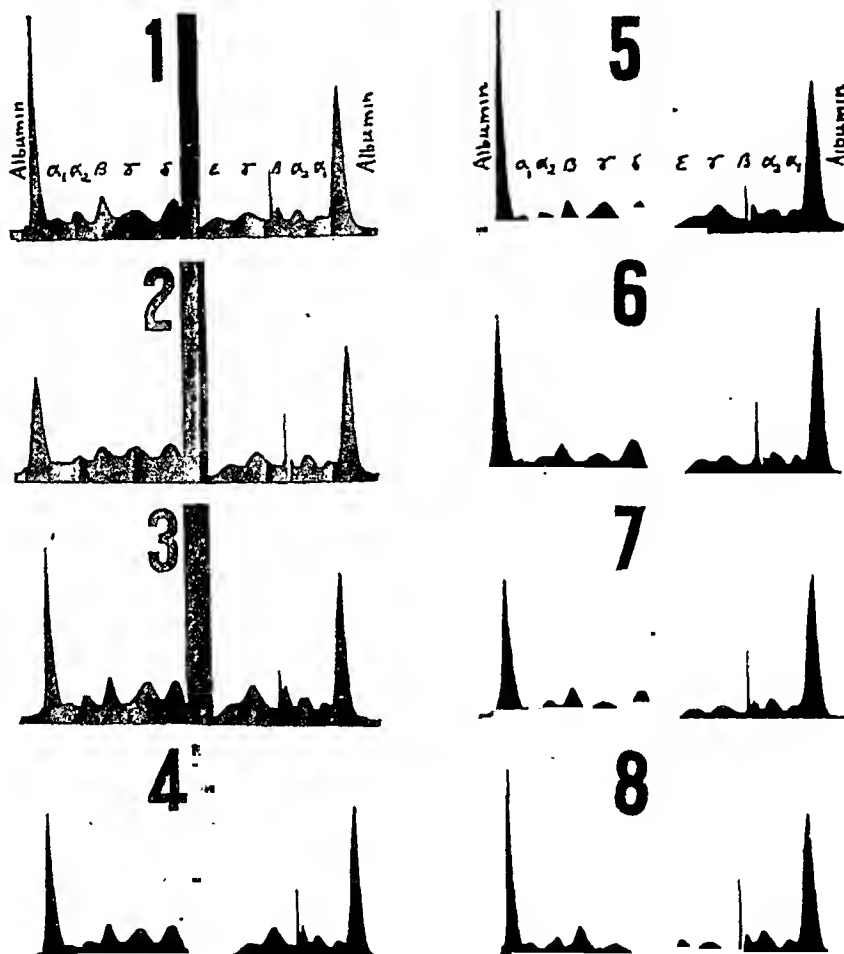


FIG. 1. Representative electrophoretic patterns. The ascending limb is to the left and the descending limb to the right in each pattern set. (1) normal, (2) untreated primary, (3) untreated secondary, (4) untreated tertiary, (5) congenital, (6) treated secondary, (7) treated tertiary and (8) biologic false-positive serum.

of evaluating such factors as the duration of treatment, age and sex on the electrophoretic pattern changes.

None of the patients included in the present series had clinical evidence of lymphopathia venereum. Frei tests were done on ten patients of the group. All were negative.

COMMENTS

The changes here observed in the electrophoretic patterns of syphilitic sera are

values. Using the ratio of each globulin fraction to albumin rather than to total protein in his computations, J. A. Cooper concluded that there was an increase in all of the electrophoretic globulin fractions. If the data of G. R. Cooper and the present observations are expressed in these terms, all globulin values appear likewise to be elevated. This method of expressing electrophoretic results, although frequently used, leads to erroneous conclusions. The

reason for this is easily seen. Ratios of globulin:albumin can change because of variation in the globulins, the albumin or in both. Thus in the case in which all the globulins remain the same but the albumin is decreased, the globulin:albumin ratios will all appear elevated. Such is essentially the situation in the electrophoretic patterns of untreated syphilitics. This explains the apparent discrepancies in the published data on syphilitic sera noted above.

In addition to the changes which have already been described the present investigations bring to light several things which have not previously been mentioned. Most striking is the return of the pattern toward normal with treatment. This occurred in most, but not all, of the treated patients. Also of interest are the variations in the alpha globulins with the various stages of the disease. A third point is the early appearance of the albumin and gamma globulin changes in the primary disease and the stability of these alterations throughout its course in the absence of treatment.

That the alterations in the electrophoretic pattern of syphilitic sera are not diagnostic and cannot be used to differentiate true syphilitic sera from so-called biologic false-positive sera has recently been shown.² The present observations support this. In addition the fact that many other diseases produce similar pattern alterations^{6,8,15} further diminishes the diagnostic importance of the changes observed in syphilis.

More important, however, than the mere recording of electrophoretic pattern alterations in disease is an attempt to interpret these changes in terms of the physiologic and biochemical significance in the organism. Such an interpretation depends upon an understanding of what the Tiselius apparatus measures, and upon some insight into the biologic function of each component measured.

In the first place, is the electrophoretic pattern a true measure of the protein components of the serum? The electrophoresis apparatus with the modern optical devices^{10,12} measures variations in the refrac-

tive index of the solution in various parts of the cell after separation of the colloidal components under the influence of an electric field. Calculations of the concentrations of the serum components have been based upon two assumptions: (1) that protein alone influences the refractivity of the dialysed serum, other substances such as lipid having no appreciable effect and (2) that all serum protein fractions have the same specific refractivity.

Recent work, however, casts some doubt upon the validity of these assumptions. It has been shown that in conditions in which serum lipoids are markedly elevated there is considerable difference between total protein values derived from the refractometric measurement in the electrophoresis apparatus and from nitrogen determination.¹⁹ Some fractions vary in this respect more than others. Thus the albumin fraction is not affected by the high plasma lipid levels and the gamma globulin is little affected, but there is a marked apparent elevation of alpha and beta globulins.

Chief alterations in syphilitic patterns are in those fractions which are little, if at all, altered by serum lipid. This, coupled with the observation that the serum lipoids are only slightly changed in syphilis,¹⁴ indicates that the pattern changes seen in untreated syphilis probably represent actual changes in protein concentration.

With regard to the biologic significance of alterations in the quantity of the components our knowledge is still meager. Assuming that the present concept of albumin production in the liver¹³ is correct, then the lowered level of the serum albumin may indicate some disturbance in this function of the liver in syphilis.

The gamma globulin fraction has been found to contain many of the known antibodies.⁵ Whether or not all of the fraction is composed of immune-body globulin is still an unsettled question.¹ A rise in gamma globulin occurs experimentally in animals following the stimulation of antibody production by a wide variety of antigens.^{17,18} Many infections or presumably infectious

diseases also produce elevations of gamma globulin.^{6,7,8,15} In the case of syphilis the rise in the gamma globulin is not accounted for by the "reagin" since specific absorption of this substance does not significantly alter the magnitude of the gamma peak.² It is possible that at least part of the increase in gamma globulin found in the syphilitic sera is in the nature of an anamnestic response and is therefore non-specific. It is evident that as yet we can arrive at no definitive conclusion concerning the significance of this elevation of gamma globulin which occurs not only in syphilis but in so many other diseases as well.

SUMMARY AND CONCLUSIONS

Using the Tiselius method of electrophoresis, studies were made on the proteins of twelve normal, thirty-two syphilitic and three biologic false-positive blood sera. The following conclusions appear warranted: (1) The serum proteins from patients with untreated primary, secondary and tertiary syphilis deviate significantly from normal. Albumin concentration is decreased and gamma globulin concentration is increased in all stages of the disease. Beta globulin is not altered. The alpha-1 globulin is significantly increased in secondary syphilis; the alpha-2 globulin is increased in secondary and tertiary syphilis. (2) Serum patterns of treated secondary and tertiary syphilitics have returned on the average to within normal limits. (3) There is a little if any correlation between positive and negative serologic reactions in syphilis and the presence or absence of electrophoretic pattern alterations. (4) The electrophoretic patterns of three patients with biologic false-positive sera exhibited changes resembling, in part, the changes found in untreated syphilitics, principally a decrease in the albumin concentration.

The possible significance of albumin and gamma globulin alterations in syphilis is discussed.

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Penicillin-resistant Non-hemolytic Streptococcal Subacute Bacterial Endocarditis*

WILLIAM H. CLARK, M.D., SERGIUS BRYNER, M.D. and LOWELL A. RANTZ, M.D.

San Francisco, California

THE first reports of the results of penicillin therapy in non-hemolytic streptococcal subacute bacterial endocarditis were not spectacular and many relapses occurred. However, only small amounts of the drug had been employed. Subsequently, with higher dosages, more and more patients have been cured, including many with "resistant" strains of streptococci. The value of supplementing penicillin therapy with anticoagulants, sulfonamides, streptomycin and renal tubular blocking substances has been considered. Various techniques for the administration of penicillin have been advocated and the duration of treatment has varied widely among different investigators.

The one point of agreement has been the realization that large daily doses of penicillin should be used in every case of this disease. Failure to control the infection with one dosage schedule requires a substantial increase in the amount of drug. Perseverance and the administration of very large to truly massive doses of penicillin have frequently resulted in the ultimate cure of patients who had suffered repeated relapses. The large supplies of highly refined penicillin now available permit the use of quantities sufficient for the cure of nearly every case of subacute bacterial endocarditis.

The purpose of this paper is to present nine cases of subacute bacterial endocarditis, treated in the Stanford University Hospitals, which have required the administration of 1 to 12 million units of penicillin daily. A résumé of the experience of other investigators with resistant endo-

carditis precedes the case reports. Brief comments concerning the individual problems encountered follow each summary, and a discussion of some of the general considerations involved in the treatment of bacterial endocarditis is presented in conclusion. No consideration will be given to factors such as pathogenesis, etiology, diagnosis or complications.

REVIEW OF THE LITERATURE

The need for administration of a million or more units of penicillin per day in the management of some of the more stubborn cases of subacute bacterial endocarditis has already been stressed by numerous investigators. Several of these studies will be mentioned to emphasize the importance of more energetic treatment after failure has repeatedly followed therapy with smaller doses of penicillin.

Dawson and Hunter^{1,2} eradicated the infection in twenty successive cases after supplies of penicillin became adequate. Failures occurred in a few of the fifteen previously treated patients. In four cases at least one course of a million or more units of penicillin per day was required. One patient, Case 16, after a total of 103 days of treatment with 200,000 to 500,000 units daily had failed, also relapsed following a period of twenty-eight days during which he received 1,000,000 units daily. Arrest of the infection was finally effected when 2,000,000 units were given daily for two weeks. Another patient, Case 17, was similarly cured when given 1,000,000 units for twelve days subsequent to 106 days of

* From the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

ineffective treatment with dosages as great as 500,000 units daily. In Case 25 the daily administration of 1,000,000 units for two weeks saw successful whereas relapse had followed treatment with 500,000 units daily for twenty days.

A different problem was encountered with Case 32. Relapse occurred after a course of treatment consisting of 500,000 units for ten days and again after 1,000,000 units had been administered daily for two weeks. A successful result was then achieved by giving 500,000 units for four weeks.

Hunter briefly mentioned four additional cases in a more recent communication.³ The first received 20,000,000 units of penicillin per day for sixteen days after multiple failures had followed treatment with daily doses of 400,000, 500,000, and 1.5, 2, 5 and 10 million units. The patient died a few weeks later of congestive heart failure, but no signs of active infection could be found at autopsy. Two patients whose infecting organisms required 1.0 unit of penicillin per ml. for inhibition *in vitro* were successfully treated with 5 and 10 million units, respectively, daily for three weeks. The fourth was a case of enterococcal endocarditis in which 8.0 units of penicillin per ml. were needed for *in vitro* inhibition. A combination of 4,000,000 units of penicillin and 4 Gm. of streptomycin given daily for four weeks apparently arrested the disease.

Mokotoff, Brams, Katz and Howell⁴ reported that large doses of penicillin were necessary in three of seventeen cases of endocarditis. Relapse and death due to the infection followed the daily administration of 1,000,000 units for fifteen days in one case. This patient had previously received smaller amounts of penicillin for 143 days. The second patient recovered when 1.2 to 3 million units per day were administered for twenty-eight days after smaller amounts of the drug had been ineffective during 117 days of treatment. A less sensitive organism was encountered in the third case. Seven days with 1,000,000 units and fourteen days with 2,000,000 units completed a continuous course of seventy-six days of therapy.

Gerber, Schwartzman and Baehr⁵ mentioned a case of enterococcal endocarditis treated with 10,000,000 units of penicillin daily for five weeks. Blood cultures remained sterile while therapy was in progress but relapse occurred one week after its completion.

Avery, Mayer and Nelson⁶ successfully treated a patient whose disease was of two years' duration. Inadequate doses of penicillin had been employed irregularly for eighteen months. The causative organism developed moderate resistance and finally required 1.4 units of penicillin per ml. of medium for inhibition. The administration of 3,000,000 units for seventeen days and then of 1,500,000 units with diodrast or para-aminohippuric acid for twenty additional days was effective.

Loewe, Rosenblatt and Altire-Werber⁷ recently presented a most unusual case of very resistant endocarditis due to *Veillonella gazogenes*. *In vitro* inhibition required 30 units of penicillin per ml. of culture medium. The patient received many weeks of treatment during which daily amounts of 500,000 to 10,000,000 units of penicillin, with and without concomitant sulfonamide therapy, were tried. A total of 466,000,000 units was administered. Then when 240 Gm. of sodium para-aminohippurate were given with 10,000,000 units of penicillin daily for sixteen days, the disease was clinically arrested.

Priest, Smith and McGee⁸ stated that their last fifteen patients have all recovered and that most of these have received at least 1,000,000 units of penicillin per day.

Morgan⁹ treated a very stubborn case of endocarditis of undetermined etiology with 20,000,000 units of penicillin for twenty days. The patient died of congestive heart failure one month after treatment was started. At autopsy the lesions of bacterial endocarditis were scarred and apparently healed.

PRESENTATION OF CASES

Selection of Cases. Thirty-three patients with subacute bacterial endocarditis have been treated on the medical service of the

Stanford University Hospitals since 1943. The first twenty-one patients, because of the scarcity of penicillin, were selected for treatment only if the causative organism required not more than 0.1 unit of penicillin per ml. of culture medium for *in vitro* in-

on a congenital septal defect was made. *In vitro* sensitivity studies revealed inhibition of the organism to be partial with 0.1 and complete with 0.2 unit of penicillin per ml. of medium.

The details of therapy and the course during the first sixty days of ineffective treatment are

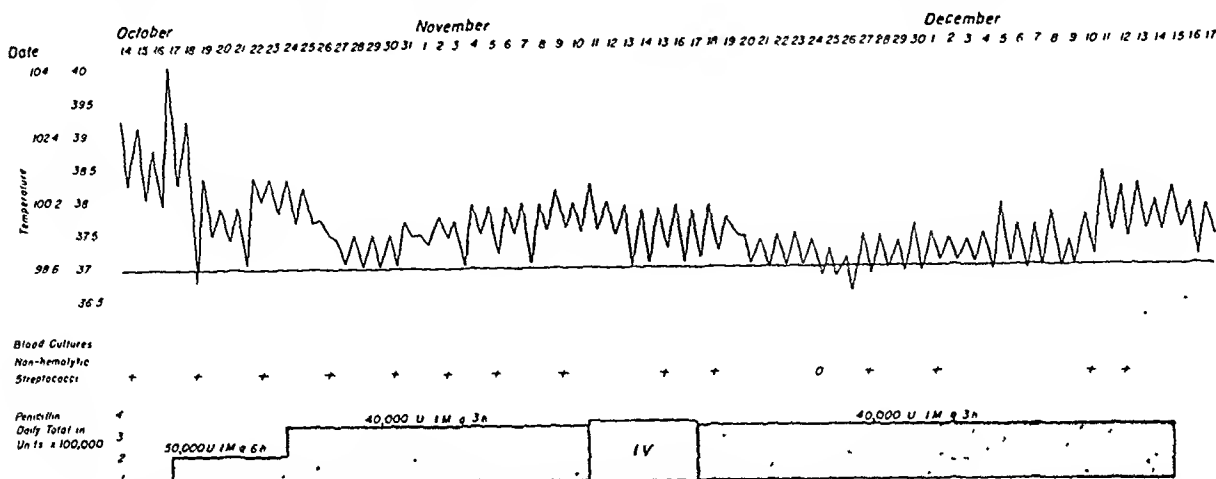


FIG. 1. Case 1, first ineffective course of therapy. Note that penicillin sensitivity data were not incorporated in this graph. There was inhibition initially by 0.1 to 0.2 unit of penicillin per ml. of medium.

hibition. These cases have been analyzed in previous reports by Bloomfield, Armstrong and Kirby,¹⁰ and by Bloomfield and Halpern.¹¹ Case 1 of the series to be presented is the last of that selected group and has previously been reported as Case 4 in the paper by Bloomfield and Halpern. Cases II through VIII are all among the last twelve consecutive and unselected cases to be treated on the medical service. Case IX has been under the care of the Department of Pediatrics and permission to include it in this group has been kindly granted by Dr. H. K. Faber.

Details of the physical and laboratory examinations, such as the presence of petechiae, splenomegaly, leukocytosis, anemia and electrocardiographic abnormalities, have been omitted from the summaries. The essential data of treatment and bacteriologic studies have been tabulated.

CASE REPORTS

CASE I. N. G., a forty-eight year old female, entered this hospital on October 14, 1944, with a febrile illness of six weeks' duration. Several blood cultures were positive for non-hemolytic streptococci, and the diagnosis of subacute bacterial endocarditis probably superimposed

shown in Figure 1 and Table 1. The patient was readmitted on January 3, 1945, after three weeks at home. Combined therapy with penicillin and sulfadiazine was unsuccessful. Definite increase in the resistance of the organism to penicillin occurred during this phase. (Fig. 2.) A successful outcome followed the use of 1,000,000 units of penicillin per day for sixty days. (Fig. 3.) She has remained free from any evidence of active infection for over eighteen months.

Comment. This case is reported for the second time as it illustrates the principal contribution of this paper, namely, that subacute bacterial endocarditis can be cured by the use of larger amounts of penicillin after many weeks of treatment have been ineffective.

The increase in the resistance of the causative organism from 0.2 to 1.0 unit of penicillin per ml. of culture medium during the period when subcurative amounts of the drug were being given should be noted.

Experience with subsequent cases indicates that initial treatment should have been with 1,000,000 units of penicillin daily as the organism was only moderately sensitive according to *in vitro* measurements.

CASE II. F. S., a sixty-nine year old male, was first seen in this clinic on August 28, 1945, with a febrile illness of four months' duration. The presence of subacute bacterial endocarditis had been suspected at another hospital but no positive blood cultures were obtained. A total

no signs of infection for twelve months since his discharge. Moderate congestive heart failure has developed but it is well controlled with digitalis and restriction of activity.

Comment. This case is not as important in regard to the purpose of this paper as the

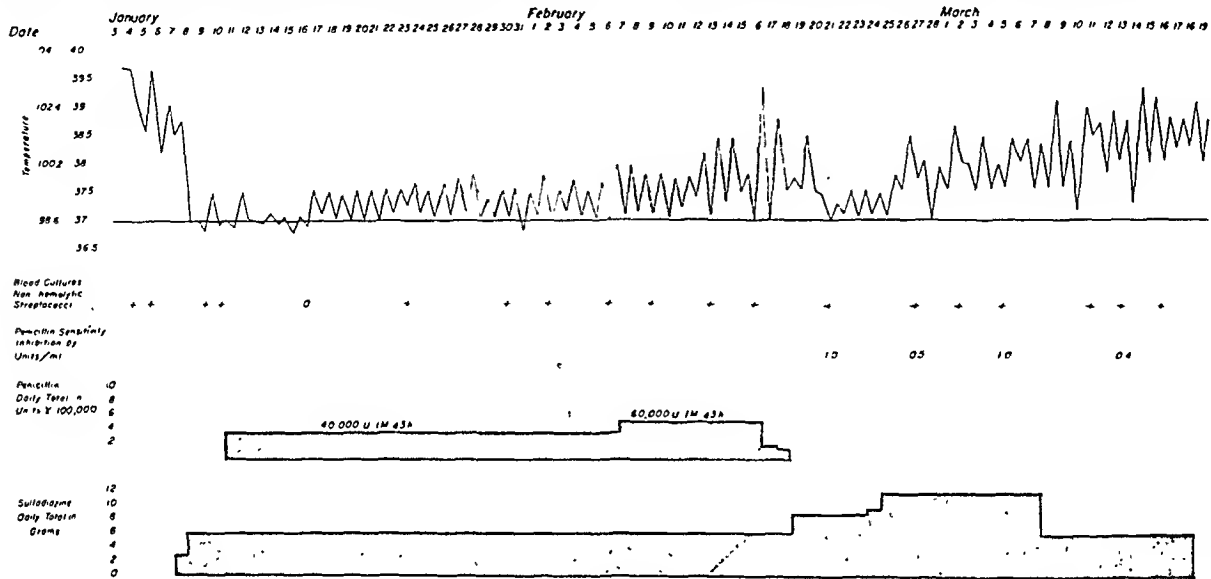


FIG. 2. Case I, second ineffective course of therapy. Note increased resistance of organism.

of 1,700,000 units of penicillin had been given in irregular doses between July 12 and August 7, 1945. The diagnosis was verified by the recovery of non-hemolytic streptococci from the blood. Sensitivity studies revealed complete inhibition by 0.2 unit of penicillin per ml. of medium. Aortic stenosis, presumably rheumatic in origin, was the underlying valvular lesion.

Therapy is outlined in the table. Interest in the efficacy of a single daily injection of a large dose of penicillin resulted in the schedule used between August 31st and October 6th. The administration of 1,000,000 units for four days was due to a misunderstanding regarding the re-evaluation of the sensitivity studies. Cultures were sterile during the first thirty-seven days of this regimen. When they again became positive, therapy was changed to a smaller daily amount of penicillin but given in seven divided doses. This was continued for twenty-three days during which time blood cultures were sterile. Relapse occurred three weeks later, after the patient had been dismissed. The *in vitro* sensitivity of the newly isolated organism was 0.1 unit per ml.

Sixty days' treatment with 1,000,000 units of penicillin daily was successful in producing clinical arrest of the disease. There have been

others because relapse followed inadequate therapy. The only conclusion possible regarding the single daily injection of penicillin is that, with the dose employed, there was failure. The organism required 0.2 unit of penicillin per ml. for *in vitro* inhibition. In accordance with current concepts, 1,000,000 units of the antibiotic should have been administered daily when therapy was first instituted.

CASE III. J. K., a thirty-nine year old male, was first seen in this clinic on October 30, 1945, with an illness of eighteen months' duration. Severe scarlet fever in March, 1944, was followed by six months of poor general health. The diagnosis of subacute bacterial endocarditis was made in September, 1944, when persistent daily fever developed, several blood cultures contained non-hemolytic streptococci and a heart murmur was noted for the first time. Penicillin was administered for more than eight weeks (Table 1) following which the patient remained quite well for three months. An attack of acute tonsillitis occurred on February 28, 1945, and the first positive blood culture in over five months was obtained ten days later. Treatment was irregular during the next ninety

days and then was allowed to lapse for four months prior to entry to this hospital.

The diagnosis of subacute bacterial endocarditis was confirmed by the recovery of non-hemolytic streptococci from several blood cultures. The penicillin concentration required

for *in vitro* inhibition and because previous treatment had not been effective.

CASE IV. G. S., a thirty-nine year old male, was first seen in this clinic on March 6, 1946, with subacute bacterial endocarditis of four

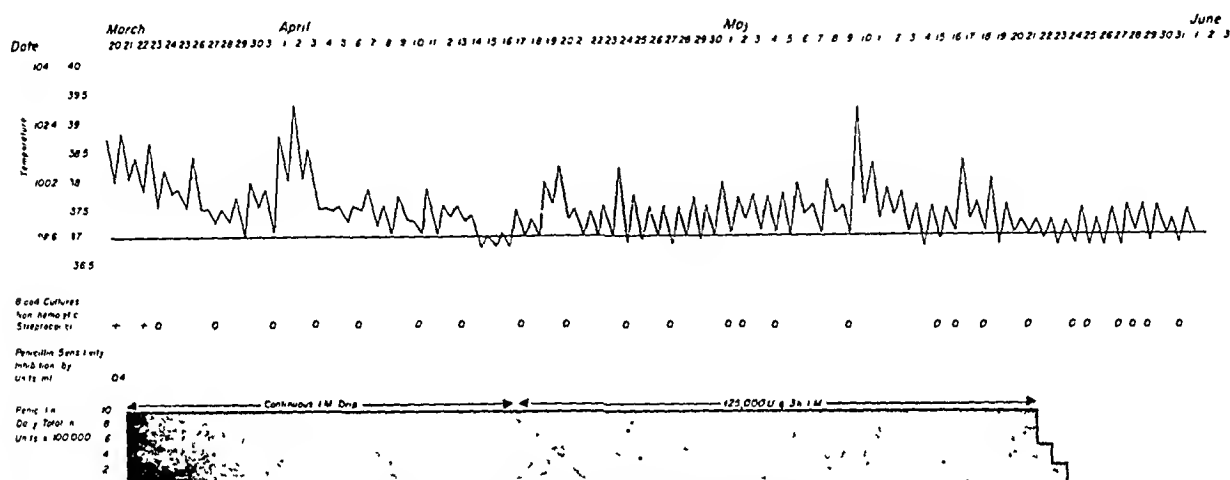


FIG. 3. Case I, curative course of therapy.

for *in vitro* inhibition was 0.4 unit per ml. The valvular lesion was that of aortic insufficiency, presumably on a rheumatic basis.

Bacterial arrest followed treatment with 1,000,000 units of penicillin for sixty days. (Table 1.) No evidence of infection has been demonstrated in the subsequent year.

Comment. Several interesting aspects of this case deserve consideration. The prolonged illness started with an attack of scarlet fever eighteen months before admission to this clinic. This acute episode was followed by six months of generally poor health. Bacterial endocarditis may have been present during this time but it seems more probable that it was a period of active rheumatic heart disease.

A definite diagnosis of subacute bacterial endocarditis was established in September, 1944, and penicillin was given for two months. No streptococci were recovered from blood cultures until after an episode of acute pharyngitis three months later. This may actually have been an instance of reinfection rather than relapse.

One million units of penicillin per day were employed because the causative organism required 0.4 unit of penicillin per ml.

months' duration. Treatment at another hospital (Table 1) had been completely unsuccessful as positive blood cultures had been obtained while therapy was still in progress. Non-hemolytic streptococci were recovered from blood cultures on three occasions prior to instituting treatment at this clinic. The *in vitro* requirement for inhibition was 0.2 unit of penicillin per ml. of medium. A congenital septal defect was the most probable anatomic cardiac lesion. Nine months after the conclusion of sixty days' treatment with 1,000,000 units daily (Table 1), there was no evidence of active infection nor of congestive heart failure.

Comment. One million units of penicillin daily were used in the treatment of this case because satisfactory results had not been obtained during ten weeks of therapy with 200,000 and 300,000 units daily. In addition the causative organism was slightly resistant to the action of penicillin as 0.2 unit per ml. was required for complete *in vitro* inhibition.

CASE V. This case is presented in more detail because of its extreme complexity. C. R., a forty-three year old male, was first seen in this clinic on March 15, 1946. There had been sudden onset of weakness and fever about a

month prior to entry and he had received 1,900,000 units of penicillin in small and irregular doses during the next thirty days. Non-hemolytic streptococci recovered from blood cultures at this hospital required 0.4 unit of penicillin per ml. of medium for complete in

preparation to a less refined product and anorexia, lassitude, nausea, vomiting, severe dizziness, fever and marked discomfort at the sites of injection developed within twenty-four hours. These symptoms became steadily worse and the use of the drug was discontinued.

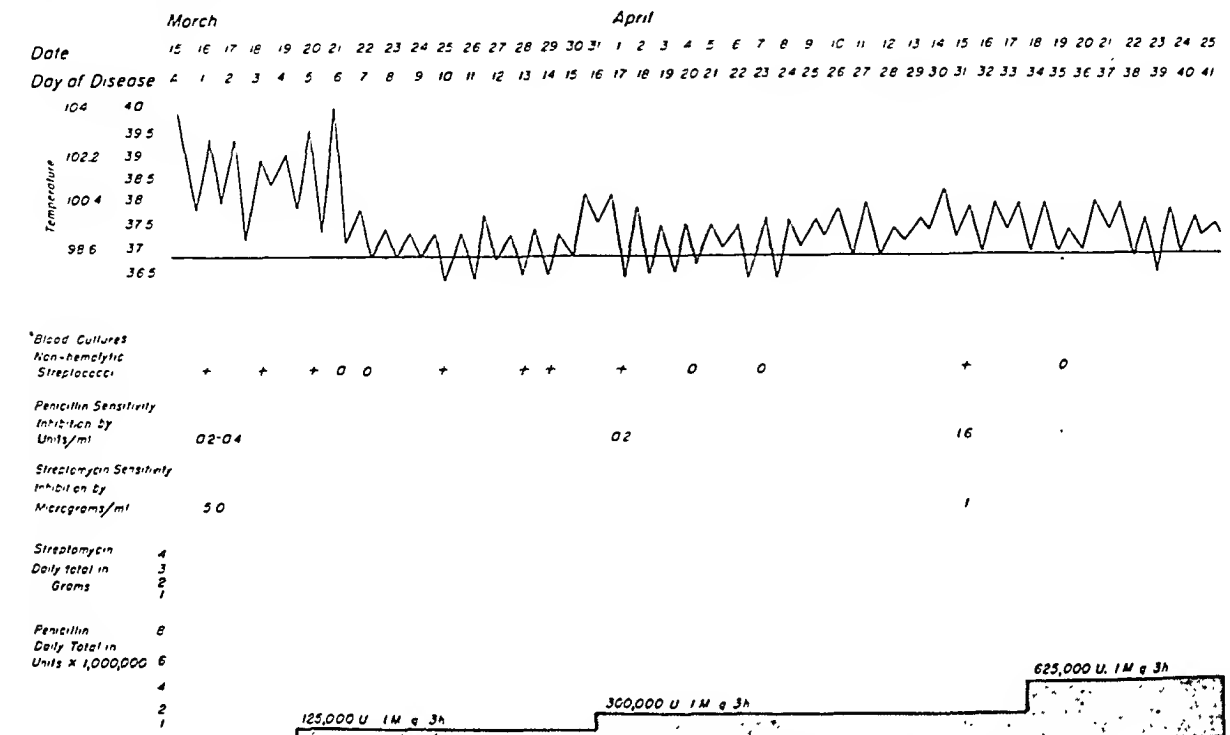


FIG. 4. Case v, initial ineffective penicillin therapy with 1,000,000 to 5,000,000 units daily.

vitro inhibition. A systolic murmur, the presence of which had been known to the patient for twenty years, was heard and some observers also detected a diastolic murmur of mitral stenosis.

The various penicillin and streptomycin dosage schedules employed and their effect on the temperature, blood cultures and sensitivity of the causative organism are given in Table 1 and in Figures 4, 5 and 6.

The patient's general condition improved greatly during the first phases of therapy with 1 to 5 million units of penicillin daily, but blood cultures were not consistently negative. The alarming increase in the resistance of the organism to penicillin and the fact that 5 micrograms of streptomycin per ml. of culture medium produced complete inhibition suggested the use of the latter agent.

There were no toxic effects resulting from the daily administration of 4 Gm. of the drug, other than mild tinnitus for fifteen days. It was then necessary to change from a highly purified

Penicillin was administered temporarily while a new supply of purified streptomycin was being obtained. Streptomycin was then employed again and no untoward reactions occurred until a different preparation was substituted seven days later. All toxic symptoms reappeared within thirty-six hours and the drug was withdrawn.

There was no antibiotic therapy during the next three weeks. The main toxic symptoms resulting from the administration of streptomycin disappeared although there was slight residual vertigo. Daily fever was present and blood cultures were positive. *In vitro* studies revealed an increase in sensitivity to penicillin, to that originally obtained. Moderate resistance to streptomycin had developed.

All toxic reactions had occurred when less highly refined preparations of streptomycin were employed and for that reason a third trial with the purified drug was made when a new supply was available. Toxic symptoms were very severe almost immediately. In addition to the effects previously mentioned, there was marked

numbness and tingling around the mouth and along the distribution of the left ulnar nerve. The use of the drug was promptly discontinued.

Bacterial arrest of the disease was finally achieved following sixty days of treatment with 8,000,000 units of crystalline penicillin daily.

of performing *in vitro* sensitivity studies before instituting treatment and frequently thereafter in cases not promptly rendered bacteria-free. The first clue suggesting that this might be a resistant case was the initial

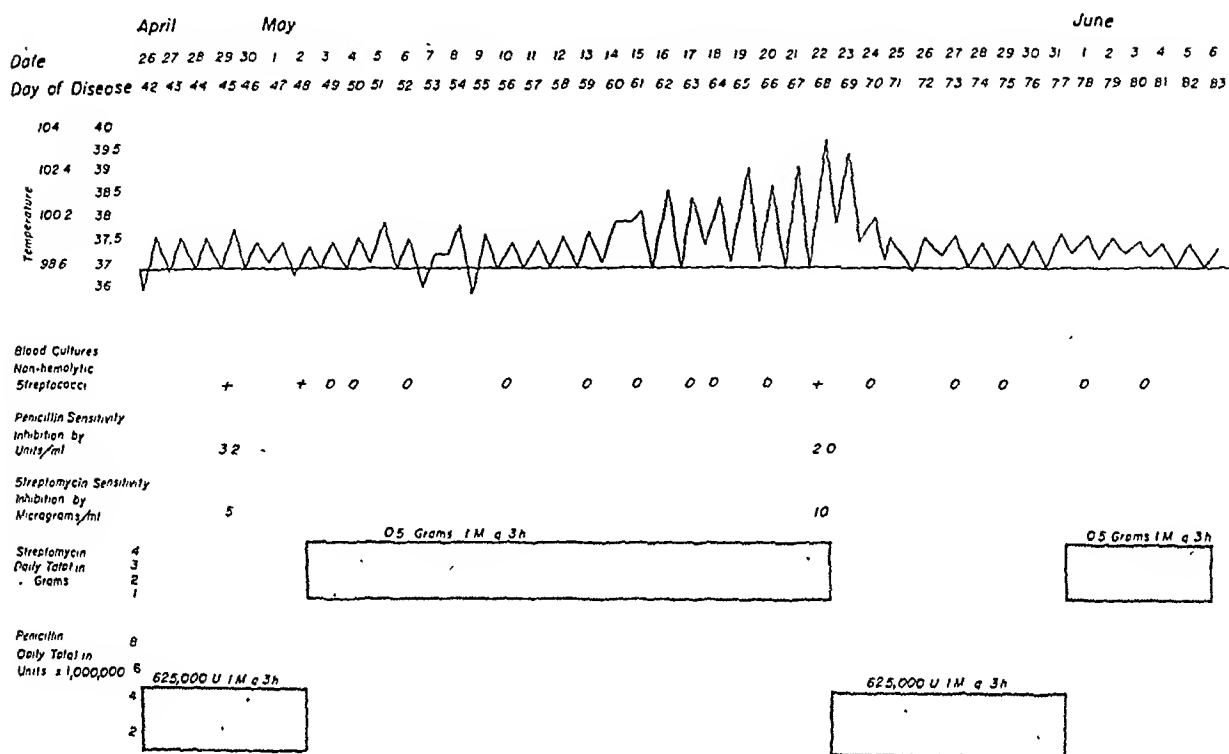


FIG. 5. Case V, ineffective streptomycin therapy. Note extreme increase in penicillin resistance.

(Fig. 6.) Sample serum penicillin levels 30, 60 and 120 minutes after an intramuscular injection of 1,000,000 units of penicillin were 10, 6.7 and 4 units per ml., respectively. These figures represent levels fifty-fold to ten-fold greater than the *in vitro* inhibiting concentration of 0.2 to 0.4 unit per ml. of medium.

This patient received 627,000,000 units of penicillin and 121.5 Gm. of streptomycin during 175 days in the hospital.* During the follow-up period of five months since discharge there has been no evidence of active infection. Minimal signs of congestive heart failure have recently been noted.

Comment. This case, without doubt, can be considered a real medical triumph. It illustrates the desirability, even obligation,

* The Commercial Solvents Corporation generously supplied large amounts of crystalline penicillin for the treatment of this patient. The streptomycin used was allocated by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

sensitivity figure of 0.2 to 0.4 unit of penicillin per ml. of medium required for inhibition. Had that information not been at hand, 1,000,000 units per day would not have constituted the starting dose and more time would have been lost with even less effective treatment. Subsequently, repeated sensitivity studies revealed a steady increase in the resistance of the organism to 1.6 and 3.2 units per ml. while 2.4 and 5 million unit daily doses failed to control the infection. Valuable information was also gained from the streptomycin sensitivity studies.

The practical aspects of giving 1,000,000 units of penicillin in a single dose intramuscularly, as when the patient was receiving 8,000,000 units daily, are important. It was necessary to use crystalline penicillin. Very little discomfort was experienced by the patient when the full amount was confined to a volume of 6 ml., of which 1 ml.

was 1 per cent procaine solution. The muscles of the thighs were utilized as well as those of the buttocks and the sites of injection were carefully rotated.

The value of giving a "rest" from penicillin administration in cases in which there

for sixty days during which time roughly 10,000,000 units had been given in intermittent intramuscular injections. Daily dosages of 400,000 units had been employed during the last three weeks. Failure was indicated by the persistence of fever and general symptoms.

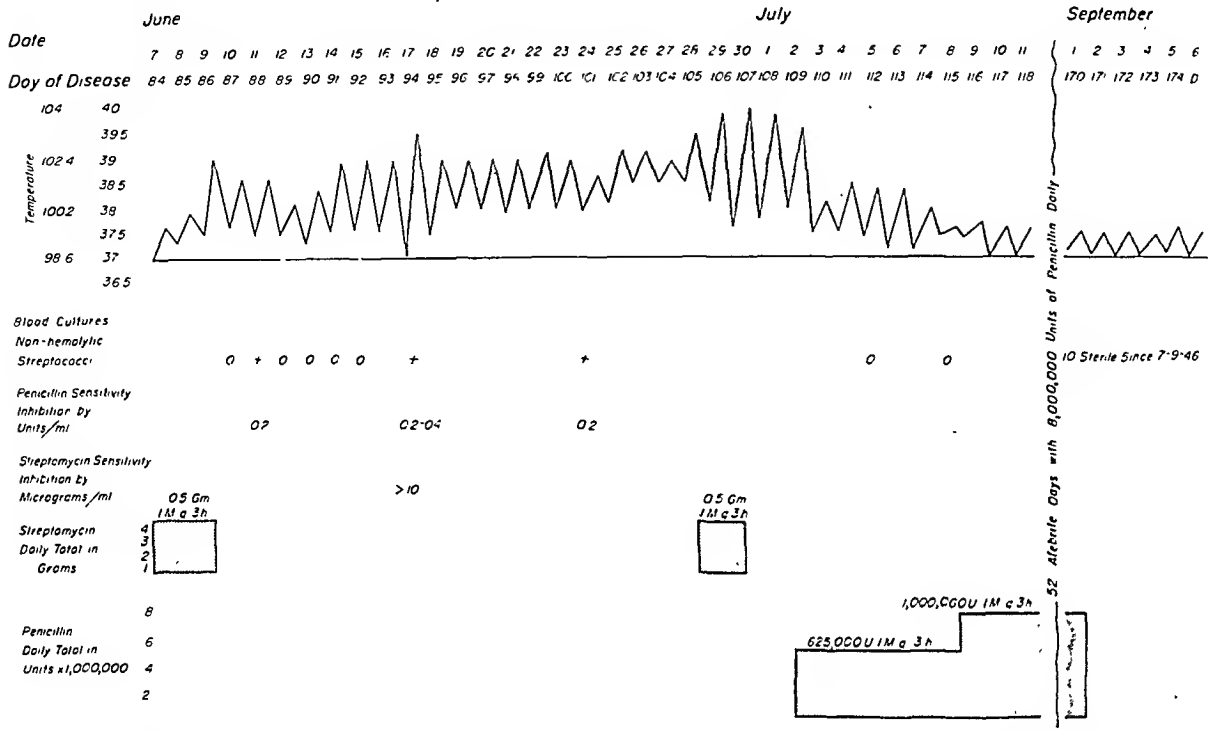


FIG. 6. Case v, curative penicillin therapy with 8,000,000 units daily. Note return to initial penicillin sensitivity.

is a marked increase in the resistance of the organism to the drug during treatment is clearly demonstrated. During a five-week period when no penicillin was administered the causative organism reverted from the high degree of acquired resistance to the original degree of moderate sensitivity. It is of interest that resistance to streptomycin was increasing meanwhile during the administration of that agent. The most important of all lessons learned from this difficult case, however, was that of the need for perseverance in spite of a long period of failure.

CASE VI. J. W., a forty-five year old male, entered this hospital on April 2, 1946, with a febrile illness of six to eight months' duration. A presumptive diagnosis of subacute bacterial endocarditis had been made elsewhere without bacteriologic confirmation in January, 1946, and penicillin had been administered fairly regularly

Non-hemolytic streptococci were recovered from the blood at this clinic. The organism required 0.4 unit of penicillin per ml. of medium for complete inhibition. A diagnosis was made of subacute bacterial endocarditis on the basis of inactive rheumatic heart disease. Therapy is indicated in Table I.

The evaluation of progress was complicated by the presence of moderate fever almost daily during treatment. Much discomfort resulted from the administration of 500,000 units of amorphous penicillin intramuscularly every three hours. This was minimized by diluting the drug in 4.0 ml. of distilled water and 1.0 ml. of 1 per cent procaine solution. Half of this was given in each thigh or buttock. Several areas of subcutaneous aseptic necrosis developed. All blood cultures taken during treatment and during the eight months' follow-up period have been sterile. The fever promptly disappeared after the administration of penicillin was discontinued. There has been no evidence of congestive heart failure.

Comment. This is a case with a moderately resistant organism. Difficulties had already been encountered in the management of Case v, who was on the ward at the same time, and the penicillin sensitivity figures were initially the same for both

and 12th. Growth occurred in forty-eight hours and *in vitro* sensitivity studies revealed complete inhibition of the organism by 0.05 unit of penicillin per ml. of medium.

Marked aortic insufficiency was indicated on entry by the blood pressure, which was 124/30,

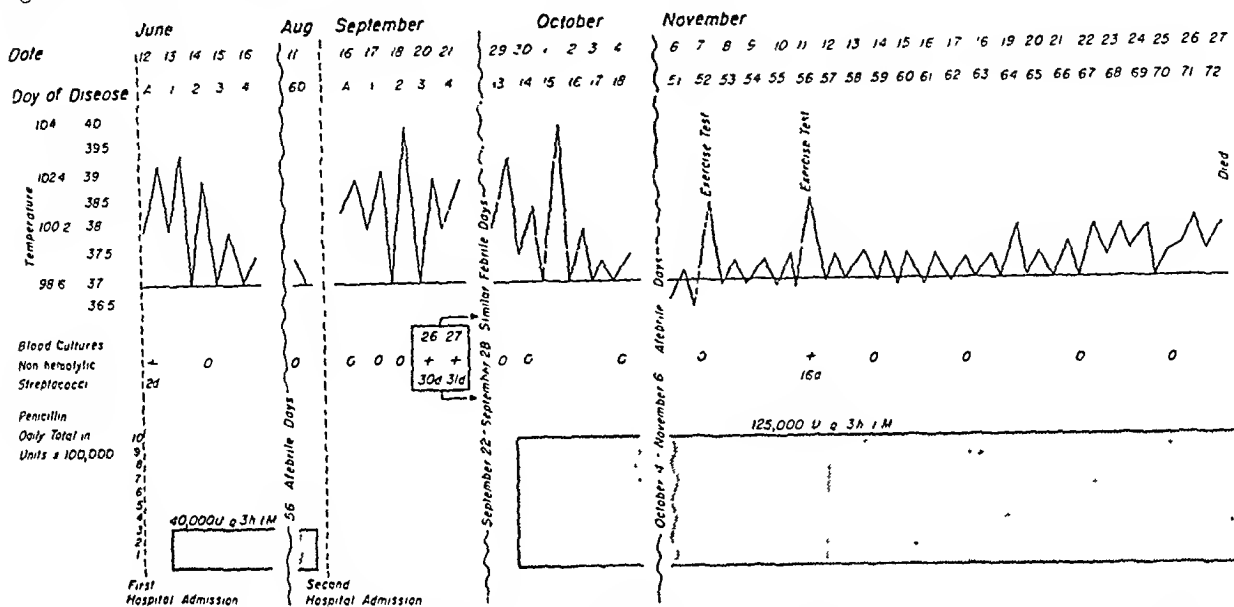


FIG. 7. Case VII, failure to eradicate infection in subacute bacterial endocarditis caused by streptococcus which was inhibited *in vitro* by 0.05 unit of penicillin. Note that sixteen to thirty-one days were required for growth of the organism in blood cultures after relapse.

cases. These influencing facts resulted in the use of 4,000,000 units of penicillin daily.

This case illustrates what others have noted, namely, that occurrence of fever during treatment, if the blood cultures are sterile, does not necessarily indicate inadequate therapy. In this instance the continued fever was probably due to the local tissue reactions resulting from the administration of large amounts of amorphous penicillin. These reactions were more severe than those experienced by other patients receiving much larger doses of crystalline penicillin (Cases v and VIII).

CASE VII. F. T., a forty-one year old male, entered this hospital on June 12, 1946, with a febrile illness of five months' duration. The patient had known that he had rheumatic heart disease. A tooth was extracted in October, 1945. The onset of fever and beginning weight loss was in January, 1946. Several blood cultures, taken in another hospital in April, were sterile.

Non-hemolytic streptococci were isolated from blood cultures at this clinic on June 8th

and by the x-ray demonstration of a moderately enlarged heart. There were no signs of congestive heart failure. Daily dosages of 320,000 units (Table I and Fig. 7) were employed as the causative organism was very sensitive to penicillin. The course during the sixty days of treatment was ideal and the patient was discharged with the disease apparently arrested.

Fever recurred two weeks later and a non-productive cough developed but blood cultures were negative. Symptoms persisted and the patient was hospitalized on September 16th. Clinically, relapse had occurred but no organisms could be recovered from the circulating blood during two weeks of observation prior to the re-institution of treatment with 1,000,000 units of penicillin per day. (Table I and Fig. 7.) There had been a further increase in the size of the heart but frank congestive heart failure was not present.

Growth appeared in two blood cultures thirty and thirty-one days after they had been taken. The organism was a streptococcus morphologically but it could not be sub-cultured and sensitivity studies were technically impossible.

Progress during the first month of the second course of treatment seemed entirely satisfactory. Penicillin serum levels were 4.0, 2.0, 0.6, and 0.4 units per ml. 30, 60, 120 and 180 minutes, respectively, after the injection of 125,000 units intramuscularly.

The first bout of nocturnal dyspnea occurred on November 4th. Râles and venous distention were present. Prompt digitalization was effective. On November 7th and November 11th graded exercise tests, using a pedal board, were given as part of a special study. Each test lasted about five minutes. A moderate chill and an abrupt transient elevation in the temperature occurred about thirty minutes after each of these. (Fig. 7.) Blood cultures were obtained during both chills and growth appeared sixteen days later in the one taken on November 11th. The organism was a streptococcus but could not be subcultured. No other blood cultures during the second course of treatment were positive.

Dyspnea became very severe on November 22nd and the patient died of congestive heart failure on November 27, 1946. At autopsy the aortic valve was found to be greatly distorted, with marked fibrosis, fusion of the commissures and shortening and perforation of the leaflets. Fresh vegetations were attached to the torn cusps. An active inflammatory process and many gram-positive cocci were demonstrated by histologic examination. Cultures made from bits of ground vegetation yielded diphtheroids and overgrowth by these contaminating organisms prevented the possible isolation of the slow-growing streptococci.

Comment. This was the only failure in the group. There was a difficult bacteriologic problem. Streptococci were recovered in forty-eight hours from blood cultures taken on entry to this clinic. Growth and subcultures were satisfactory. The original sensitivity figure of 0.05 unit of penicillin per ml. of medium therefore seems perfectly valid. After relapse had occurred no growth was detected in blood cultures until there had been thirty days of incubation. The advisability of keeping all cultures for at least a month before discarding them as sterile is illustrated.

The well known fact that the prognosis must be extremely guarded while treatment is in progress is exemplified by this case. The

clinical response was ideal during the entire sixty-day period of initial therapy. The temperature fell quickly to normal and blood cultures were repeatedly sterile.

Penicillin in amounts greater than 1,000,000 units per day should, perhaps, have been used since there were incomplete data about an organism which had resisted earlier treatment. The clinical response during the first month of the second course of penicillin therapy was also very satisfactory and hence misleading. The single positive blood culture obtained during the course of treatment, because of its very slow growth, gave information too late to permit a further increase in the penicillin dosage prior to death.

CASE VIII. C. G., a fifty-four year old male, entered this hospital on June 21, 1946. Fever, weakness and weight loss had been present since May, 1945. The diagnosis of subacute bacterial endocarditis, due to an enterococcus, was made at another hospital in May, 1946. A congenital septal defect was considered to be the underlying abnormality. Treatment with 300,000 and 800,000 units of penicillin daily was given during the four weeks prior to transfer to this hospital.

Non-hemolytic enterococci (*Streptococcus faecalis*), requiring 10.0 units of penicillin per ml. of culture medium for inhibition, were recovered from the blood. There was evidence of a diffuse renal lesion. The following data were derived from a timed urine examination with Addis count: specific gravity 1.013, total protein excretion 0.3 Gm. per twenty-four hours, 1,000,000 casts per twenty-four hours, 98,000,000 white and epithelial cells, and 44,000,000 red blood cells per twenty-four hours. Phenol-sulfonphthalein excretion was 27 per cent in two hours. The blood urea concentration was 66 mg. per 100 ml.

Crystalline penicillin* was used exclusively for treatment, 12,000,000 units per day being administered. (Table 1). The last thirty days of therapy were received at a hospital of the Veterans' Administration. Thirty minutes after an intramuscular injection of 1,500,000 units, serum levels were as high as 100 units per ml.,

* A large quantity of crystalline penicillin was donated by the Commercial Solvents Corporation for the treatment of this patient.

and two hours later, 20 to 50 units per ml. were still present.

An erythematous macular rash developed on two occasions during therapy. This promptly disappeared following the administration of benadryl.

The clinical response was prompt and sustained. There has been no evidence of active infection during the six months since the completion of therapy. The status of the renal lesion, however, remains in doubt. The blood urea has remained slightly elevated, the last determination being 53 mg. per 100 ml. Urinary protein excretion has decreased from 0.3 to 0.09 Gm. per twenty-four hours but the patient's blood pressure has progressively risen from 130/78 to 190/118. There has been no evidence of congestive heart failure.

Comment. The causative organism in this case was an enterococcus (*Streptococcus faecalis*) requiring 10.0 units of penicillin per ml. for *in vitro* inhibition. Truly massive daily amounts of penicillin must be administered in order to obtain serum concentrations of the drug adequate to affect such an extremely resistant organism. Doses of 8,000,000 and 12,000,000 units per day were employed with success. Due to moderate renal insufficiency, serum penicillin levels were several-fold greater than are usually obtained with comparable doses. It is probable that arrest of the disease might not have been achieved had renal function been normal.

CASE IX. R. F., a nine year old schoolboy, entered the pediatric service on October 17, 1946, with a febrile illness of ten days' duration. Non-hemolytic streptococci were recovered from blood cultures. *In vitro* inhibition was complete in a concentration of 0.05 unit of penicillin per ml. of medium. The boy was moderately cyanotic and congenital pulmonic stenosis without other anatomic abnormalities was demonstrated by angiograms.

Treatment with 400,000 units of penicillin daily for fifty-one days (Table 1) was accompanied by prompt clinical response. All blood cultures were sterile. The child was discharged one week after the completion of therapy.

Two blood cultures, taken two and four days, respectively, after the last injection of penicillin were positive nine days later. The slow growing

organism was morphologically a streptococcus but it could not be subcultured. No penicillin sensitivity studies were possible.

Moderate fever was present when the child was re-admitted on December 21, 1946. Penicillin therapy was re-instituted and the daily dosage increased to 2,000,000 units. (Table 1.) The duration of treatment was twenty-four days. There was occasional low-grade fever while therapy was in progress but blood cultures were consistently negative. All blood cultures have been sterile for eight weeks following the conclusion of treatment.

Comment. This boy weighed only 23 Kg. so the initial daily dose of 400,000 units of penicillin was very liberal. The organism was highly sensitive to penicillin. Treatment was prolonged and the clinical course ideal but relapse occurred within two days. The cultural characteristics of the streptococcus recovered had changed greatly; growth was slow and subculturing impossible.

The recent experience with Case VII had been very similar and it was of great influence in reaching the decision to increase the daily dose of penicillin five-fold and continue treatment for only three weeks. It is still much too early to know how successful such a regimen may have been. This is another instance in which apparent arrest of the disease during active therapy was very misleading.

COMMENT

Penicillin Dosage. Dosage schedules, as proposed in some of the more encouraging of the earlier reports of penicillin therapy in subacute bacterial endocarditis,^{1,10,12,13} were of necessity restricted because small supplies of the drug were available. Only cases with very sensitive causative organisms could be effectively treated. These reports indicated that penicillin in daily doses of 100,000 to 300,000 units was effective in a large percentage of the cases and, until about the middle of 1945, it was believed that 300,000 units comprised an adequate initial daily dosage. Subsequently, numerous patients were cured only when larger amounts of the drug were employed.

TABLE I

Case No.	Patient Sex, Age	Primary Cardiac Disease	Probable Duration of Infection *	Infecting Organism		Penicillin Dates of Therapy	Penicillin				Duration of Follow-up	Remarks								
				Type	Inhibition by Penicillin (units/ml.)		Dose in Units and Route	Total Units Daily	No. of Days	Total per Course and Patient										
I	N. C. F., 48	Congenital? Septal defect?	6 weeks	Non-hemolytic streptococci	0.2 0.4 0.5 1.0 0.5	a.	10/17/44-10/24/44	50,000 q 6 h I.M.	200,000	8	20 mo.	Recovered; no cardiac symptoms								
							10/25/44-11/8/44	50,000 q 4 h I.M.	300,000	15										
							11/9/44-11/16/44	400,000 I.V. drip	400,000	7										
							11/17/44-12/16/44	40,000 q 3 h I.M.	320,000	30										
							11/17/44-12/16/44	40,000 q 3 h I.M.	320,000	30										
II	F. S. M., 69	Rheumatic, aortic stenosis	4 months	Non-hemolytic streptococci	0.2	b.	1/10/45-2/8/45	40,000 q 3 h I.M. + S.D. 6 Gm./d.	480,000	7	12 mo.	Recovered; congestive heart failure; 10 mo. digitalized								
							2/9/45-2/16/45	60,000 q 3 h I.M. + S.D. 6 Gm./d.												
							2/17/45-2/19/45	20,000 q 3 h I.M. + S.D. 9 Gm./d.	160,000	3										
							2/17/45-2/19/45	20,000 q 3 h I.M. + S.D. 9 Gm./d.	160,000	3										
							c.	3/21/45-4/15/45	1,000,000 I.M. drip	1,000,000	26		24,000,000							
							4/18/45-5/18/45	125,000 q 3 h I.M.	1,000,000	34	33,750,000									
							a.	(another hospital) 7/12/45-8/7/45	I.M.—divided doses	100,000 to 125,000			160	89,570,000						
							b.	8/31/45-9/13/45	500,000 I.M.—single dose	500,000	14		1,700,000							
								9/14/45-9/17/45	125,000 q 3 h I.M.	1,000,000	4									
								9/18/45-10/6/45	500,000 I.M.—single dose	500,000	19									
III	J. K. M., 39	Rheumatic, aortic insufficiency	18 months	Non-hemolytic streptococci	0.2 0.1		10/7/45-10/29/45	30,000 q 3 h I.M. X 7	210,000	23	22,245,000									
							12/7/45-2/5/46	125,000 q 3 h I.M.	1,000,000	60		60,000,000								
							a.	(another hospital) 9/26/44-12/8/44	I.M.—divided doses	120,000-200,000	145		83,945,000							
								3/20/45-7/2/45 (irregular)	I.M.—divided doses	240,000-300,000	74	9,210,000								
							b.	11/13/45-1/13/46	125,000 q 3 h I.M.	1,000,000	103	?								
IV	G. S. M., 39	Congenital? Septal defect	4 months	Non-hemolytic streptococci	0.2					60	60,000,000	13 mo.	Recovered; no cardiac symptoms							

TABLE I—(Continued)

Case No.	Patient Sex, Age	Primary Cardiac Disease	Probable Duration of Infection*	Infecting Organism		Penicillin Dates of Therapy	Penicillin				Duration of Follow-up	Remarks
				Type	Inhibition by Penicillin (units/ml.)		Doses in Units and Route	Total Units Daily	No. of Days	Total per Course and Patient		
v	C. R. M., 43	Rheumatic; Mitral	1 month	Non-hemolytic streptococci	0.2-0.4 1.6 3.2 SM ¹ -5 mμ 2.0 SM ¹ -5 mμ-10 mμ 0.2-0.4 SM ¹ > 10 mμ	a. 3/20/46-3/31/46	125,000 q 3 h I.M.	1,000,000	12	11,625,000	5 mo.	Recovered; minimal congestive heart failure
						b. 4/1/46-4/17/46	300,000 q 3 h I.M.	2,400,000	17	40,800,000		
						c. 4/18/46-5/1/46	625,000 q 3 h I.M.	5,000,000	14	70,000,000		
vi	F. T. M., 41	Rheumatic, aortic and mitral	5 months	Non-hemolytic streptococci	0.05 (see text)	h. 5/2/46-5/22/46	0.5 Gm. q 3 h I.M.	4.0 Gm.	21	81.5 Gm.	Died, congestive heart failure 8 mo.	Cocci in vegetations at autopsy
						i. 5/22/46-5/30/46	625,000 q 3 h I.M.	5,000,000	9	45,000,000		
						j. 6/1/46-6/8/46	0.5 Gm. q 3 h I.M.	4.0 Gm.	8	32.5 Gm.		
vii	J. W. M., 45	Rheumatic type?	9 months	Non-hemolytic streptococci	0.4	k. 6/9/46-6/27/46	No treatment	4.0 Gm.	3	7.5 Gm.	Recovered; increasing hypertension with mild renal insufficiency	Recovered
						l. 6/28/46-7/1/46	0.5 Gm. q 3 h I.M.	5,000,000	7	35,000,000		
						m. 7/2/46-7/8/46	625,000 q 3 h I.M.	8,000,000	54	425,000,000		
viii	C. G. M., 54	Congenital septal defect	13 months	Enterococcus (Streptococcus faecalis)	10.0	n. 7/9/46-9/1/46	1,000,000 q 3 h I.M.	1,000,000	145	627,425,000 - SM ¹ -121.5 Gm.	Recovered	Recovered
						o. 6/12/46-8/11/46	40,000 q 3 h I.M.	320,000	60	19,200,000		
						p. 10/1/46-11/27/46	125,000 q 3 h I.M.	1,000,000	58	58,000,000		
ix	R. F. M., 9	Congenital pulmonic stenosis	10 days	Non-hemolytic streptococci	0.05 (see text)	q. (another hospital) Feb.-Mar., 1946	Divided doses	200,000 to 400,000	118	77,200,000	6 mo. bacteria free	Recovered
						r. 4/2/46-4/6/46	40,000 q 3 h I.M.	320,000	60	10,000,000+		
						s. 4/7/46-4/10/46	125,000 q 3 h I.M.	1,000,000	5	1,600,000		
x	C. G. M., 54	Congenital septal defect	13 months	Enterococcus (Streptococcus faecalis)	10.0	t. 4/7/46-4/10/46	500,000 q 3 h I.M.	4,000,000	47	183,120,000	6 mo. bacteria free	Recovered
						u. 4/11/46-5/27/46	I.M.—divided doses	300,000	116	198,720,000+		
						v. (another hospital) May-June, 1946	I.M.—divided doses	800,000	21	6,300,000		
xi	R. F. M., 9	Congenital pulmonic stenosis	10 days	Non-hemolytic streptococci	0.05 (see text)	w. 6/22/46-7/1/46	1,000,000 q 3 h I.M.	8,000,000	7	5,600,000	2 mo. bacteria free	Recovered
						x. 7/2/46-8/21/46	1,500,000 q 3 h I.M.	12,000,000	10	80,000,000		
						y. 10/19/46-12/7/46	50,000 q 3 h I.M.	400,000	51	19,800,000		
xii	R. F. M., 9	Congenital pulmonic stenosis	10 days	Non-hemolytic streptococci	0.05 (see text)	z. 12/23/46-12/24/46	125,000 q 3 h I.M.	1,000,000	2	1,500,000	2 mo. bacteria free	Recovered
						aa. 12/25/46-1/15/47	250,000 q 3 h I.M.	2,000,000	22	42,150,000		
									75	63,450,000 -		

* When seen in this clinic.
 1.—Streptomycin sensitivity—micrograms per ml. of medium.
 SM.—Streptomycin.
 S.D.—Sulfadiazine.
 I.V.—Intravenous.
 I.M.—Intramuscular.

Until recently insufficient data had been accumulated to permit any correlation between studies of the *in vitro* penicillin sensitivity of the causative organism and the response to therapy. It is now known that such tests, at best, are not always reliable guides to treatment but they usually provide valuable information. The technics employed vary in different laboratories. Caution must be exercised when evaluating the results of such studies done by workers inexperienced in these procedures.

There is, nevertheless, fairly general agreement that organisms which are inhibited by 0.1 unit or less of penicillin per ml. of culture medium may be considered sensitive. Those requiring 0.2 to 0.4 unit per ml. are classified as moderately sensitive, and those requiring 0.5 to 5, 10 or more units as moderately to very resistant. Fortunately, about 90 per cent of all non-hemolytic streptococci (*Streptococcus viridans* is included in this group) fall into the sensitive group.¹⁴ The enterococcus (*Streptococcus faecalis*) is always very resistant. Most investigators believe that serum penicillin levels of four to eight times the concentration required for *in vitro* inhibition of the organism should be obtained for effective treatment. Data have been accumulated by which serum penicillin levels can be crudely estimated in advance for various doses given by different routes.

Initial daily penicillin dosage schedules derived from the *in vitro* sensitivity of the causative organism may be proposed on the basis of information obtained in the treatment of subacute bacterial endocarditis in this and other clinics.^{3,5,14,15,16} Patients with sensitive organisms should receive at least 500,000 units of penicillin daily. If 0.2 to 0.4 unit of penicillin per ml. of culture medium is required for inhibition, the administration of 1 to 2 million units per day is advised. Most patients with organisms inhibited by about 1.0 unit per ml. require 5,000,000 units daily.

The necessary dose for the treatment of cases with very resistant organisms is difficult to estimate. The enterococcus

(*Streptococcus faecalis*) is most frequently encountered in this group and occasionally concentrations of 50 to 100 units per ml. are required for *in vitro* inhibition. It is doubtful whether patients with such excessively resistant organisms can be cured with any practicable amounts of penicillin. Fortunately, most enterococci are inhibited by 5 to 10 units per ml. and the administration of 10 to 20 million units of penicillin per day may well be followed by a satisfactory result. No published reports of the daily use of more than 20,000,000 units of penicillin have appeared, but there is no reason to believe that larger amounts cannot be given if warranted by the clinical situation.

Therapeutic failures in patients with subacute bacterial endocarditis treated with dosage schedules derived from *in vitro* penicillin sensitivity values will continue to occur from time to time. These will be less frequent, however, when there is a rational guide to the initial management, especially when it has been found that the organism is not highly sensitive. Difficulties in treatment can then be anticipated and therapy scaled upward as indicated. All of the cases reported in this paper, except vii and ix, are examples of the usefulness of such knowledge. The exceptions illustrate how *in vitro* tests may be misleading. The causative organisms were apparently most sensitive but treatment was unsuccessful. These failures further emphasize the advisability of using 500,000 or more units of penicillin daily for all patients even though many can be cured with smaller amounts.

It is difficult to estimate the dosage of penicillin which is required when the circulating blood is not sterilized promptly or in patients who have relapsed. The *in vitro* sensitivity of the organism may help in arriving at a decision. Occasionally a definite increase in resistance has occurred. More prolonged treatment with the same inadequate daily dose is not often effective. Drastic increases of five- to ten-fold are advised for every case failing to respond to therapy. Some patients will be overtreated

but this is necessary if the maximal number of recoveries is to be obtained.

Organisms are occasionally encountered which are slow growing and difficult to subculture. Sensitivity studies are then technically impossible. This problem was encountered in Cases VII and IX after relapse had occurred. Whenever bacteriologic information is incomplete, very large amounts of penicillin should be given.

Mention should be made at this point of the identification by Loewe, Plummer, Niven and Sherman¹⁷ of a newly recognized strain of non-hemolytic streptococcus, tentatively called *Streptococcus s.b.e.* Loewe and Altire-Werber have described cases of subacute bacterial endocarditis due to this strain.¹⁸ Apparently the organism is sensitive to the *in vitro* action of penicillin but is resistant to treatment. The organisms recovered from the nine cases reported have been studied from the standpoint of the cultural and biochemical characteristics described for this strain of streptococcus. None could be fitted into this classification.

Route of Administration. There is disagreement in regard to the route of choice for the administration of penicillin. The advantages of continuous intravenous or intramuscular infusion as compared to intermittent intramuscular injections have been widely discussed. Fairly constant serum levels are maintained at all times during the continuous administration of penicillin; their magnitude depends on the total daily dose. Much higher serum levels, on the other hand, are obtained for thirty to sixty minutes after each single injection when the same daily amount of penicillin is given in multiple divided doses. The more effective route cannot be determined at present as not enough is known about the fundamental mechanism of the action of penicillin on bacteria in the body.

An attractive hypothesis is strongly emphasized by Gerber, Schwartzman and Bachr⁵ who believe that the very high (as great as 500 times the *in vitro* inhibiting concentration in the case of very sensitive organisms) serum penicillin levels obtained

by giving a "booster dose" twenty minutes after a regularly scheduled injection allow better penetration of the drug into the depths of the vegetations.

There are fewer technical difficulties for the attendants, and the patients are afforded a much greater degree of freedom when the intermittent injection method is used. The criticism that large single doses are poorly tolerated by the patient has been largely overcome by the use of crystalline penicillin. In Case VIII the patient received 1,500,000 units in each injection. Procaine was added to the solution and there was very little local discomfort.

The suggestion has been made³ that the more simple intermittent intramuscular injection method be used initially in the treatment of subacute bacterial endocarditis but that continuous drip therapy should be employed if results are not satisfactory. All of the patients included in this paper except Case I were treated solely with multiple injections of penicillin.

An additional observation indicates that a twenty-four-hour effective serum penicillin level is not necessary. Although failure occurred when the patient in Case II was treated with a single injection of 500,000 units daily, another patient was clinically cured when 200,000 units were given twice a day for eight weeks. The course was as satisfactory in every way as that of others treated with a similar amount of penicillin in eight smaller doses daily.

It is probable that the route of administration is not important. Good results with all methods have been obtained by satisfying the fundamental requirement that enough penicillin be given during each twenty-four-hour period.

Geiger and Goerner¹⁹ recently presented an encouraging preliminary report on the use of penicillin in oil and beeswax in the treatment of three patients with endocarditis. More information is needed before the widespread use of this preparation can be recommended. It is to be anticipated that its administration will be limited to patients

requiring relatively small daily amounts of penicillin.

There seems to be no place for penicillin given orally in the therapy of subacute bacterial endocarditis since it is neither an economical nor a sure method. Five to ten times the parenteral dose must be administered by mouth in order to obtain comparable serum penicillin levels. Absorption is irregular, undependable and varies greatly in its relation to meals.

Duration of Therapy. It has been difficult to establish an optimal period of treatment for subacute bacterial endocarditis. Autopsies have been done on numerous cases in which the active infectious process apparently had been arrested prior to death due to some other cause. Analysis of the findings reveals much variation in the time required for complete healing of the vegetations. Cocci have been found by microscopic examination of the vegetations as long as three months after the completion of sixty consecutive days of penicillin therapy.²⁰ These have been located in small areas of necrosis and leukocytic infiltration deep in scarred and nearly healed lesions. It is of interest that cultures prepared from ground portions of these vegetations were sterile.

In contrast, other investigators^{3,4,21} have not been able to demonstrate the presence of bacteria in lesions examined a few weeks after the conclusion of treatment with comparable daily amounts of penicillin given for only two to four weeks.

It is difficult to know how much importance should be attached to the knowledge that bacteria may still be present in the heart valves weeks after the infection has been clinically controlled. Accumulating evidence suggests that relapse usually occurs within days or a very few weeks of the time treatment has been stopped. If this is true, persisting foci of organisms surrounded by scar tissue may not be indicative of ultimate recurrence of the infection.

Since the study of the anatomic end result does not furnish the answer, the pooling of experience with many cases must be the

guide in determining the adequate period of treatment. Evidence is now at hand which suggests that the critical factor is the dose of penicillin employed. Numerous cases have been reported in which failure has followed the administration of increasing but inadequate amounts of the drug for long periods. Then, when penicillin in quantities adequate for that particular case was given, a few days of treatment were sufficient. Some striking examples have been cited in the review of the literature previously presented.^{2,3,4,7,9}

The prolonged periods of treatment given to the patients discussed in this paper now seem excessive. Those that responded promptly probably would have been cured with much briefer therapy. On the other hand, those that required multiple courses of penicillin with increasing dosages were not treated soon enough with the daily amount of penicillin required to arrest the infection. It is of utmost importance that the required curative daily dosage be employed at the earliest possible time. This will minimize the dangers of the development of increased penicillin resistance of the organism and of additional deformity of the valve during prolonged subcurative therapy. Every patient with streptococcal subacute bacterial endocarditis should receive 500,000 or more units of penicillin daily as indicated by the organism's sensitivity. The period of treatment should be approximately four weeks. This regimen will be followed by arrests of the infection in nearly all cases.^{2,3,22,23,24,25} Difficult problems will be recognized much more quickly, and drastic increases promptly made in the daily amount of penicillin used if the duration of the initial course has been no longer than one month.

SUPPLEMENTARY THERAPEUTIC MEASURES

Anticoagulants. The use of heparin and, to a lesser degree, dicumarol in the therapy of endocarditis was advocated first in the era of the sulfonamide treatment of this disease. Shortly after the advent of penicillin therapy evidence indicated that benefit was derived

from the combined use of penicillin and heparin.¹² Subsequent reports, however, have revealed that no advantage is gained from the use of anticoagulants.^{2,11,14} A recent communication⁸ added what should be the final argument against the necessity or even advisability of employing these drugs. There was no lower incidence of embolic phenomena and, of greater importance, fresh fibrin deposits on the diseased heart valves were demonstrated at autopsy in patients who received heparin. The nature of these findings, when added to the dangers of uncontrolled hemorrhage, increased technical difficulties and much greater expense, definitely argues against anticoagulant therapy in this disease. It has been suggested that small amounts of heparin, such as 50 mg., when incorporated in a day's supply of infusion fluid may be of help in preventing local clotting in the needle and adjacent vein during continuous intravenous therapy. This is a particularly useful procedure when para-aminohippuric acid or diodrast is given.^{6,7}

Renal Tubular Blocking Substances. Substances that interfere with the excretion of penicillin by kidney tubules have been employed in order to obtain higher serum levels without increasing the dose of penicillin. It has been shown that the simultaneous administration of penicillin and sodium para-aminohippurate or diodrast by continuous infusion maintains serum levels several-fold greater than those obtained when penicillin is given alone.^{26,27,28} Striking clinical applications of these methods have been reported.^{6,7} These preparations have not been extensively used because they are expensive and require continuous infusion. In order to overcome this last objection, benzoic acid has been administered orally.^{21,29} Serum levels were obtained comparable to those to be expected from doses of penicillin six to ten times as great if given alone.

The encouraging effects derived from the use of these renal tubular blocking substances has led to further research in an effort to discover others. Clinical investiga-

tions with caronamide (4'-carboxy-phenyl-methanesulfonanilide), a new oral drug, are currently in progress.³⁰

Streptomycin. Because of the widespread use of streptomycin in infections due to gram-negative organisms, its effectiveness against gram-positive cocci is not appreciated. Many strains of streptococci and staphylococci are relatively susceptible or very sensitive to the action of this antibiotic.

Whenever a case of subacute bacterial endocarditis caused by a resistant organism is encountered, sensitivity studies with streptomycin should be done. The combined use of the two drugs may be effective when either given alone is not. The case of enterococcal endocarditis previously mentioned is an illustrative example.³ The ultimate eradication of the infection in Case v was accomplished by the use of penicillin but it is not unreasonable to assume that benefit was derived from the administration of streptomycin.

Prophylaxis. The administration of sulfonamides and penicillin at the time of tooth extraction, tonsillectomy and operative genitourinary procedures in all cases of known valvular or congenital heart disease is an accepted prophylactic measure against the possible development of subacute bacterial endocarditis. An adequate program has not yet been established. Hunter²³ reports the disease following tooth extraction in a patient who had received full doses of sulfadiazine and 25,000 units of penicillin every three hours for two days. He and his colleagues now give 100,000 units every three hours with full doses of sulfadiazine for two days, and then continue the sulfadiazine alone for several additional days.

CONCLUSIONS

The infectious process can be arrested in nearly every case of non-hemolytic streptococcal subacute bacterial endocarditis if enough penicillin is administered in each twenty-four-hour period. Nine cases have been presented, each of which has received

from 1 to 12 million units of the antibiotic daily. Eight patients have recovered.

Some definite recommendations for the treatment of this disease have been derived from the analysis of these cases and from those reported by others. The *in vitro* penicillin sensitivity of the causative organism should, if possible, be determined before therapy is instituted. The initial daily dosage of penicillin should be based on these studies. Cases with sensitive organisms should receive at least 500,000 units per day. When the causative organism is moderately or markedly resistant, 1, 5, 10 or even 20 million units should constitute the daily dosage.

The duration of therapy should be approximately four weeks. More prolonged therapy is usually unnecessary if adequate amounts of penicillin are used, and increased resistance of the organism to penicillin may develop under prolonged subcurative dosage.

The daily penicillin dosage should be drastically increased five- to ten-fold if the circulating blood is not promptly sterilized after treatment has been started or if relapse occurs subsequent to its completion. There will be instances of unnecessarily intensive therapy but arrest of the infection should more nearly approach 100 per cent.

The drug may be effectively administered by continuous drip or intermittent intramuscular injections. The latter method is more simple and very large individual doses of crystalline penicillin can be given with minimal local discomfort. The use of anticoagulants is not indicated. Streptomycin may advantageously be used alone or simultaneously with penicillin in some very resistant cases.

ADDENDUM

One year after submitting this article, all eight of the living patients remain free from any evidence of recurrent infection.

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Expulsion of Group A Hemolytic Streptococci in Droplets and Droplet Nuclei by Sneezing, Coughing and Talking*

MORTON HAMBURGER, JR., M.D. and O. H. ROBERTSON, M.D.

Cincinnati, Ohio

Chicago, Illinois

THE number of group A beta hemolytic streptococci† which carriers expelled into sterile handkerchiefs when they sneezed, coughed or blew their noses was determined in investigations among army personnel in 1944 and 1945.¹ These studies revealed that nasal carriers frequently discharged hundreds of millions of hemolytic streptococci into handkerchiefs when blowing their noses. Sneezing expelled far fewer, the output of single sneezes of throat carriers ranging from none to 106,000 and of nasal carriers from none to 50,000,000. Most coughs were entirely free of these bacteria although rare coughs dispersed 40,000 to 50,000.

Although these experiments afforded information about the maximum number of hemolytic streptococci which might be discharged by the three respiratory activities studied, they gave no indication as to whether organisms sneezed or coughed were propelled through the air far from the carrier, whether they were largely contained in heavy droplets which fell rapidly to the floor, or whether they remained floating about in the form of "droplet nuclei."² Furthermore, in several instances the hemolytic streptococci recovered from handkerchiefs held over the mouth during sneezing (nasal and oral sneeze discharges were collected in separate handkerchiefs) greatly

exceeded the total numbers which could be accounted for by the atomization of many cc. of the carrier's saliva, the beta streptococcal content of which had been ascertained. It seemed likely that this discrepancy could be explained by contamination of the mouth handkerchief with non-atomized secretions which issued from the nose during sneezing. Thus it appeared that the number of hemolytic streptococci propelled directly into the air in either heavy or light droplets might be much smaller than the number collected by a handkerchief held over the mouth.

Although sneezing and severe coughing are not ordinarily important symptoms of streptococcus carriers,^{1,3} it nevertheless seemed desirable to amplify the earlier studies in order to ascertain how many streptococci may actually be expelled into the air during these activities as well as by talking, a more common although less violent exercise. Studies of this nature were made possible by the availability, at the University of Chicago, of rooms especially designed⁴ for the investigation of air-borne infection, and by the cooperation of the members of Epidemiology Unit No. 13 at the Great Lakes Naval Training Station who provided the subjects.

These experiments seemed particularly desirable because there are no recorded data upon the expulsion of any respiratory pathogen in the form of tiny droplet nuclei which may remain suspended in the air. Because of the ease with which it can be

† The terms group A streptococci, beta hemolytic streptococci and hemolytic streptococci are used interchangeably in this paper and indicate group A hemolytic streptococci.

* From the Commission on Air-Borne Infections, Army Epidemiology Board, Office of the Surgeon General, United States Army, and the Department of Medicine, University of Chicago, Chicago, Ill.

identified in air cultures, beta hemolytic streptococcus is a particularly satisfactory micro-organism with which to initiate investigations of this important problem. Bloomfield and Felty⁵ in 1923, and later Paine,⁶ Hare,³ Duguid⁷ and ourselves¹ investigated the number of beta hemolytic streptococci expelled by coughing, talking or sneezing upon blood agar plates, but since a blood agar plate collects a disproportionately large sample of rapidly falling particles as opposed to "droplet nuclei,"⁸ it yields little or no information about the latter. Hare³ hoped he had overcome this objection by placing plates in front of the subject at different angles from the vertical, but even this technic does not dispose of the possibility that very tiny particles may not stick to the plate.

During the winter of 1945 to 1946 we carried out a series of experiments with two objects in view: (1) to determine the numbers of group A hemolytic streptococci expelled directly into the air by sneezing, coughing and talking, and (2) to differentiate between streptococci contained in rapidly falling droplets, and tiny droplet nuclei which remain in the air for longer periods of time. It is the purpose of this communication to describe these investigations.

MATERIAL AND METHODS

Subjects. The carriers were young men between seventeen and twenty years of age undergoing primary (boot) training at the Great Lakes Naval Training Station, Illinois. They were detected by nose and throat culture surveys made by the personnel of Epidemiology Unit No. 13. Carriers exhibiting nose and throat cultures strongly positive for hemolytic streptococci or else strongly positive throat but negative nose cultures were selected for study. A few cultures were only moderately or weakly positive. Some of the carriers had been recently hospitalized for tonsillitis or pharyngitis, others had reported to sick call but had not been hospitalized and still others denied symptoms of recent respiratory infection.

Plan of Experiments. The subject, who wore a clean surgical gown, was seated in a chair in the corner of a 640 cubic foot glass-walled room,

the dimensions of which were 8 by 10 feet by 8 feet high. He faced the opposite corner. The door of the room was closed and the fan customarily employed to mix the air was not run. Six air cultures (Fig. 1) were taken, as follows: (1) Three large blood agar plates (154 sq. cm. area) containing 1:1,000,000 gentian violet were placed on the floor directly in front of the subject, one 1.5, one 5.5 and one 9.5 feet from the vertical plane of his face. Large rapidly falling droplets would be expected to fall on these "settling plates," particularly the one nearest the subject. (2) In order to capture tiny "droplet nuclei" which might remain in the air longer and not settle on the plates during the course of the experiment, three broth bubbler samplers of the type described by Lemon⁹ were set up 1.5, 5.5 and 9.5 feet from the subject's face, mounted on ring stands with the air inlets 3 feet from the floor. These samplers draw air through 20 cc. of broth at the rate of 1 cubic foot a minute; at the end of the experiment 5 cc. aliquots of the broth were used for making blood agar pour plates containing 1:1,000,000 gentian violet, a concentration which permits alpha and beta hemolytic streptococci to grow while suppressing most staphylococci and other gram-positive saprophytes.

Immediately before the experiment, nose and throat swab cultures were made on each subject as well as quantitative cultures of the saliva, the hands and of sterile handkerchiefs into which they blew their noses. At the beginning of the experiment the investigator opened the plates, left the room, closed the door and gave the subject a signal from outside to sneeze, cough or talk. As soon as the respiratory activity being tested began the pumps used to draw air through the bubbler samplers were turned on from outside the room. The samplers were run for five minutes. The subject then left the room and in some of the sneezing and coughing tests fresh samplers were substituted for the first six. The second set of samples was started eight to eleven minutes after the first sneeze or cough. In a few tests the air was also sampled at twenty minutes, thirty minutes or three hours after the beginning of the experiment.

Sneezing. Sneezing was induced by the powdered seedpods of the prickly nightshade (*Solanum elaeagnifolium*).¹ The powder was placed on a small piece of gauze and sniffed into the nostrils by the subject. One to twenty-four sneezes were induced in five minutes in

susceptible subjects but many failed to sneeze at all.* The carriers were instructed to try to sneeze in a horizontal direction and if possible not to lower the head. This instruction was practically always adhered to. They were also cautioned not to cover the sneeze with the hand

and size of beta streptococcus-containing droplets they produce is shown by the data of Table 1 and illustrated diagrammatically in Figure 2. Four more or less distinct bacteriologic patterns were found among the twenty subjects investigated, although

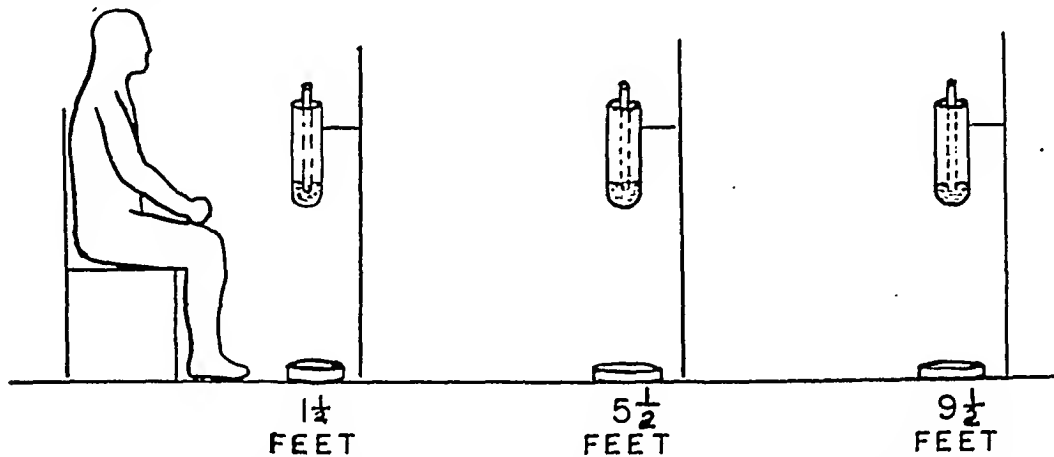


FIG. 1. Arrangement of subject and samplers during tests of sneezing, coughing and talking in experimental room. The blood agar plates on the floor captured large, rapidly falling droplets during the five-minute test. The "bubbler samplers," whose inlets were on a level with the carrier's face, captured tiny "droplet nuclei."

or handkerchief although a well developed reflex required voluntary control in every instance.

Coughing. Subjects were instructed to cough violently twelve times in a horizontal direction. It was observed that most of the men coughed from the back of the mouth and did not tend to approximate the teeth or lips.

Talking. Subjects counted out loud for five minutes, reaching 200 to 400 in this time. Since the numbers from one to one hundred include many beginning with F, S and T, three of the four syllables known to produce the largest number of droplets,¹⁰ the test was weighted to some extent in favor of the greatest expulsion of bacteria.

Typing of Streptococci. The serologic type of beta hemolytic streptococci in the nose or throat of the carriers was determined by the staff of Epidemiology Unit No. 13 by the method of Swift, Wilson, and Lancefield.¹¹

EXPERIMENTAL RESULTS

Cultures of the Air during Sneezing. That sneezes vary considerably in the number

* M. J. Green had previously observed that sneezing was more easily induced in carriers whose nose cultures were positive than in those exhibiting negative nose cultures. This suggests that the irritating effect of the powder is greater on an inflamed than on an uninfamed mucous membrane.

the sneezes all looked very much alike to the observer stationed outside the room. In the most common pattern (65 per cent of the subjects) few or no beta streptococci were discharged as droplet nuclei, but many were expelled in large droplets captured by the settling plate on the floor 1½ feet from the subject. Fewer than 10 per cent of these large droplets travelled as far as 5½ feet. In a less common pattern, (A in Table 1), 10 per cent of the subjects, small numbers of droplet nuclei contained beta streptococci but none were collected in large droplets falling on the settling plates. In 20 per cent of the subjects, (B in Table 1), few or no beta streptococci were recovered at all.

Only one carrier, No. 20, sneezed large numbers of beta streptococci (and also alpha streptococci), both as droplet nuclei and in large droplets falling on all three settling plates. That this subject was really an unusually good atomizer was shown by a second test performed six days after the first. In these two tests he expelled an average of nine beta streptococci per cubic foot per sneeze as droplet nuclei fairly evenly

TABLE I

BETA HEMOLYTIC STREPTOCOCCI EXPELLED INTO AIR DURING INDUCED SNEEZING
The Most Common Pattern—Most Beta Streptococci Fell to the Floor $1\frac{1}{2}$ Feet from Sneezer; Very Few Were Discharged in the Form of Droplet Nuclei

Carrier No.	TC	RN	LN	Saliva BHS per cc.	No. of Sneezes	Droplet Nuclei BHS per cu. ft. of air per sneeze.* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate per sneeze. Distance from Carrier, Feet		
						$1\frac{1}{2}$	$5\frac{1}{2}$	$9\frac{1}{2}$	$1\frac{1}{2}$	$5\frac{1}{2}$	$9\frac{1}{2}$
1	++	0	++	2	2.2	0	0.4	1.0	0	0
2	+++	+++	+++	470,000	6	0.3	0	0.6	1.5	0	0
3	+++	+++	+++	1,340,000	1	0.8	1.6	0	15.0	3.0	1.0
4	+++	++	+++	2,880,000	2	0.4	0.8	14.5	0.5
5	+++	+++	+	1,720,000	5	0.5	0	0	11.2	0	0
6	++	+	+++	70,000	1	0	0	0.8	11.0	1.0	0
7	+++	0	0	86,000	2	0	0	0	5.0	0	0
8	+	0	++	440,000	2	0	0	0.4	29.0	2.5	0.5
9	+++	+++	+++	31,000	3	0.5	0	0	2.7	0	0.3
10	+++	+++	+++	2,070,000	7	0.1	0.1	0	6.0	0	0
11	+	0	+++	420,000	24	0.5	0.1	0	22.0	1.4	0
12	++	++	+	80,000	3	0.3	0.3	0	6.3	0.7	0
13	+++	+++	+++	290,000	6	0.2	0.5	0.3	66.6	0.8	0

Less Common Patterns—A. More Than One Streptococcus per Cubic Foot of Air as Droplet Nuclei But None in Large Droplets

14	++	+++	++	4	1.5	0.9	0.7	0	0	0
15	+++	+	0	290,000	1	1.2	1.2	1.2	0	0	0

B. Very Few Streptococci Expelled in Any Form

16	+	+	+++	prob. 0	3	0	0	0	0.3	0.3	0
17	++	+	+++	800,000	1	1.0	0	0	0	0	0
18	?0	++	++	?2,000,000	7	0	0	0	0.5	0	0
19	+	0	+++	500,000	1	0.8	0	0	0	0	0

Rare Pattern—Very Large Numbers of Streptococci Discharged in Both Large Droplets and Droplet Nuclei

20†	++	0	0	7,560,000	7	10.3	7.8	3.1	86.8	65.7	23.2
20	+++	0	+	3,230,000	9	10.4	14.5	6.4	508.3	64.4	12.9
20	+++	+	++	1,200,000	4	0	0	0	32.5	1.3	0.3

TC = Throat culture

RN = Culture of right nostril

LN = Culture of left nostril

BHS = Beta hemolytic streptococcus

* Air cultured by bubbler samplers (9).

† Three separate tests were performed on Carrier No. 20 on different days

Streptococcus Types:

Type 19; cases 1, 3, 5, 8, 9, 11, 14, 15, 16, 18

Type 17; cases 6, 7, 19

Type 3; cases 10, 12, 13, 20

Not 3, 17 or 19; cases 4, 17

Nose and throat cultures were graded as follows:

+++—strongly positive

++—moderately positive

—weakly positive

0—negative for beta hemolytic streptococci

distributed among the three bubblers. In a third experiment the following week his output diminished. He apparently combined the quality of efficient atomization with an inordinately high beta streptococcal contamination of the saliva, exhibiting the

Table II. The most important difference between the sneeze patterns of alpha and beta streptococci was that although the discharge of great numbers of beta streptococci as droplet nuclei was rare, the expulsion of large numbers of alphas in this form

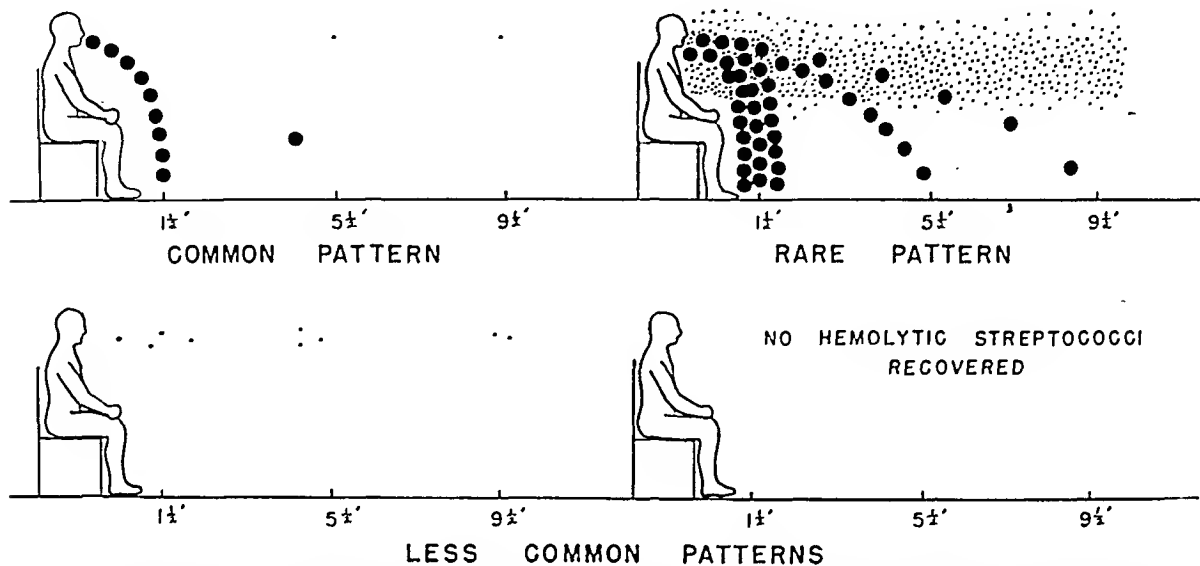


FIG. 2. Patterns of expulsion of beta hemolytic streptococci by carriers during sneezing. The exaggerated heavy dots represent large droplets which fell rapidly to the ground and were collected by settling plates. The small dots represent "droplet nuclei" which remained suspended in the air for longer periods of time. The "less common pattern" on the left is referred to in the text as "A"; that on the right as "B."

second highest contamination of any sample measured during three years' observations.

Alpha Streptococci and "Total Bacteria." In addition to the beta streptococci, green-forming colonies (salivary streptococci) were usually counted in the pour plates made from bubbler air samples as were the total number of colonies (exclusive of beta streptococci) on the gentian violet blood agar plates exposed on the floor. Although usually more than 80 per cent of the colonies on these settling plates were small green pigment producers, there were also some staphylococci and other micro-organisms which were not identified. For the purposes of this discussion it will be assumed that green-forming colonies in bubbler samples and most of the "total bacteria" on the settling plates were alpha streptococci. Only a negligible error is introduced by this assumption.

The numbers of these non-pathogens recovered from the air are presented in

was common, occurring in 35 per cent of the subjects. Most of the remaining 65 per cent expelled few or no alphas as droplet nuclei but significant numbers in large droplets. Thus the common and rare patterns but not the less common patterns of beta streptococcus expulsion were reproduced by alpha streptococci. The relations of these observations to the concentration of alpha and beta streptococci in the saliva will be discussed later in the paper.

Uniformity of Distribution of Droplet Nuclei Sneezed into the Experimental Room. Nearly as many droplet nuclei were recovered 5½ and 9½ feet from the sneezer as 1½ feet away. This distribution was in striking contrast with that of the larger droplets, 90 per cent of which travelled only 1½ feet. Figure 3 compares the number of alpha streptococci captured by bubblers and settling plates, using the counts at 1½ feet as one hundred. The figure includes all carriers who expelled as many as ten alpha strepto-

cocci per cubic foot of air per volley of sneezes.*

Persistence of Alpha and Beta Streptococci in Air after Sneezing. The persistence of alpha and beta streptococci as droplet nuclei after large droplets have left the air is illustrated

TABLE II
ALPHA STREPTOCOCCI AND TOTAL BACTERIA EXPELLED
DURING INDUCED SNEEZING

Carrier No.	No. of Sneezes	Droplet Nuclei Alpha Streptococci per cu. ft. of Air per Sneeze. * Distance from Carrier, Feet			Large Droplets Bacteria per Settling Plate per Sneeze. Distance from Carrier, Feet		
		1½	5½	9½	1½	5½	9½
19	1	189.0	224.0	197.0	438.0	91.0	98.0
7	2	53.5	41.5	158.5	2500.0	168.0	140.0
13	6	23.5	39.5	21.8	629.3	127.3	63.5
12	3	66.0	37.3	15.3	401.3	58.3	17.6
20	7	28.1	13.0	5.2	TMC	128.1	121.7
	9	10.7	21.6	4.2	TMC	77.3	32.2
	4	163.5	16.2	8.5
5	5	10.6	9.0	6.0	248.8	36.8	8.4
16	3	28.3	5.6	2.6	18.6	12.0	1.3
8	2	7.5	3.0	7.0	76.0	5.2	3.0
9	3	4.0	2.0	532.0	31.3	23.0
18	7	1.4	2.5	0.7	11.0	1.4	0.5
4	2	3.0	3.5	190.0	1.5
1	2	1.4	1.4	3.4	6.0	0	4.0
6	1	3.0	0	0.8	45.0	6.0	1.0
17	1	0	0	3.0	59.0	7.0	2.0
3	1	58.0	15.0	13.0
11	24	0	0	0	1.7	0.2	0
10	7	0	0	0	42.8	0.4	0.7
2	6	0.2	0	0.6	1.5	0	0
14	4	6.2	0	0
15	1	9.0	4.0	5.0

TMC = Too many to count

* Air cultured by bubbler samplers*

The carriers in this table are the same as those in Table I

by the data of Table III. This table presents cultures made during sneezing and eleven to sixteen minutes after the first sneeze, i.e., after the subject had left the room. Five experiments from two carriers are included. Two points seem worthy of comment. First, approximately 50 per cent of the

* The same distribution maintained for beta streptococci although only one carrier expelled significant numbers of these organisms in the form of droplet nuclei.

number of streptococci collected during sneezing still remained suspended in the air ten to sixteen minutes. Air cultures made in one experiment thirty minutes after the first sneeze, not included in the table, revealed only 5 per cent left. The pooled data of several other experiments in which only small numbers of streptococci were expelled substantiate the findings in the two carriers discussed previously. Our findings are in general agreement with those of Bourdillon, Lidwell and Lovelock,¹² who noted that of the total number of air-borne bacteria recovered during the first minute after sneezing, 32 per cent were present fifteen minutes later.

The second point of interest in Table III is the sharp change in the distribution of the streptococci on the three settling plates ten to sixteen minutes after sneezing as compared with the sneezing period. During sneezing, about ten times as many streptococci were collected in the nearest settling plate as in either of the other two whereas the three plates exposed ten to sixteen minutes after sneezing recovered approximately equal numbers. This means that the plates in the postsneezing period probably collected particles of the same order of size as did the bubblers during sneezing. Once the rapidly falling droplets had left the air, settling plates collected small droplets or droplet nuclei which had become evenly dispersed throughout the room and settled slowly to the floor.

Effect of Baffling a Sneeze with the Hand. The effect of baffling a sneeze with the hand tested by carrier No. 20, the only subject who dispersed large numbers of beta hemolytic streptococci. In a volley of nine sneezes he expelled eleven per cubic foot per sneeze (as droplet nuclei). In this volley the settling plates at 1.5, 5.5 and 9.5 feet collected 508, 64 and 13 beta streptococci, respectively, per sneeze. The alpha streptococci and total bacteria followed the same pattern although they were more numerous than the beta streptococci.

About fifteen minutes later in a different room he sneezed three times, covering his

mouth and nose with his hand. In contrast with the un baffled sneezes two of the bubblers recovered no bacteria and the third only 0.8 beta and 1.6 alpha streptococci per cubic foot for the volley of three sneezes. Except for three colonies of beta strepto-

from the posterior pharynx. It is possible that this represented secretion which descended from the nose for a sterile handkerchief into which he blew his nose (not in the experimental room) shortly before the test yielded 24,000,000 beta streptococci. On

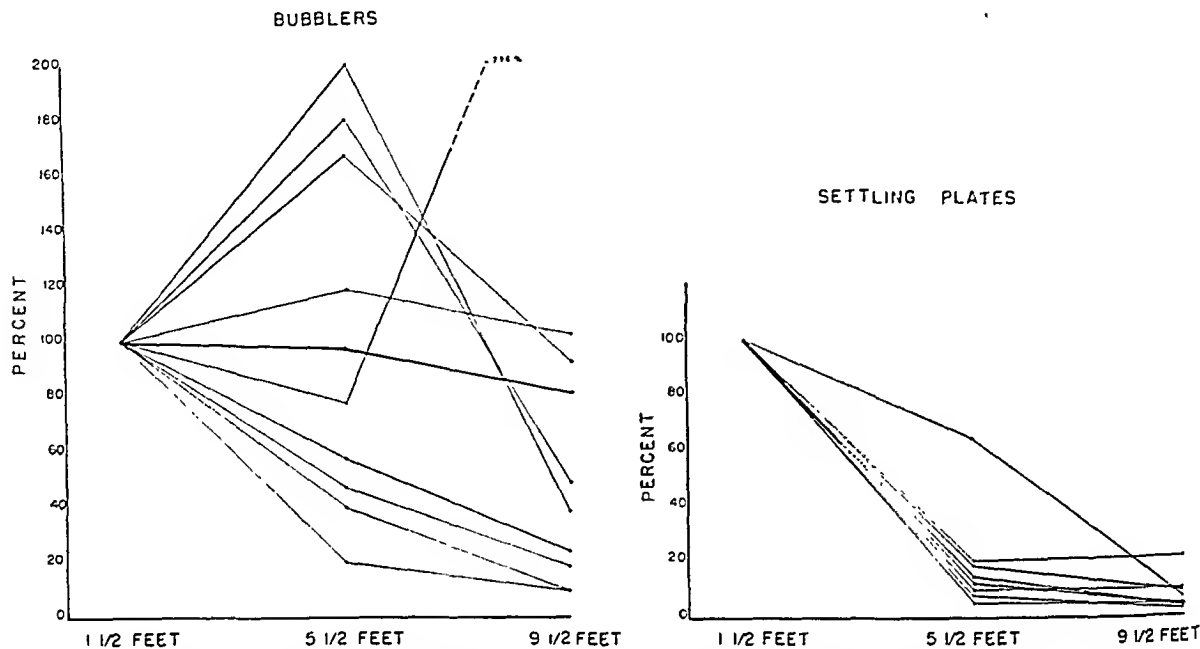


FIG. 3. Recovery of alpha streptococci expelled during sneezing at various distances from the sneezer. The number of alpha streptococci recovered 1½ feet from each subject is represented as 100 per cent. Each experiment is represented by one curve on each graph. The heavy line on the bubbler graph represents the average of the nine experiments. On the settling plate graph there are eight instead of nine individual curves because two are superimposed.

cocci in the nearest settling plate no bacteria of any kind were recovered by plates.

Coughing. Practically no beta streptococci were coughed out by nineteen of the twenty carriers presented in Table iv. Sixty per cent expelled none at all in either droplets or droplet nuclei in volleys of ten to seventeen vigorous un baffled coughs. Thirty-five per cent dispersed fewer than one per cubic foot in any of the three bubbler samples, and only one or fewer in the nearest settling plate.

One carrier, No. 21, expelled very large numbers, averaging 4 per cubic foot per cough, or 45 per cubic foot during the volley of twelve coughs. Quite large numbers were recovered by both bubblers and plates 5½ and 9½ feet from the cougher. Interestingly enough the air contained no alpha streptococci, indicating that the fluid coughed was not saliva but rather material

the other hand, his saliva contained only 38,000 per cc. Further evidence that the saliva is not ordinarily the fluid which comprises cough droplets was the absence of alpha streptococci in the air in nearly all the other cough tests.

Talking. Almost no beta (or alpha) streptococci were expelled during talking. (Table v.) No bubbler sample collected as many as one streptococcus per cubic foot, and twenty-nine of the thirty samplers in tests of ten carriers captured none at all. The settling plates likewise were practically free of streptococci, only three of thirty plates exhibiting one colony each.

COMMENTS

Dispersion of a particular pathogen by any respiratory activity, such as sneezing, coughing or blowing the nose, will depend upon the nature of the secretion discharged

TABLE III
PERSISTENCE IN AIR OF DROPLET NUCLEI SNEEZED INTO THE EXPERIMENTAL ROOM

Carrier No.	No. of Sneezes	Kind of Streptococcus	Time of Cultures in Relation to Sneezing	Streptococci in Droplet Nuclei per cu. ft. Air per Volley of Sneezes* Distance from Carrier, Feet			Streptococci Collected on Blood Agar Plates on the Floor Distance from Carrier, Feet		
				1½	5½	9½	1½	5½	9½
7	2	Alpha	During sneezing; 10-15 min. after	107 146	83 140	317 160	5,000 58	336 60	280 50
20	7	Beta	During sneezing; 11-16 min. after	72 38	55 34	22 24	608 42	460 27	163 29
20	7	Alpha	During sneezing; 11-16 min. after	197 45	91 35	37 15	6,000 196	879 168	852 132
20	9	Beta	During sneezing; 11-16 min. after	94 18	131 50	58 22	4,575 44	580 41	116 38
20	9	Alpha	During sneezing; 11-16 min. after	97 19	195 36	38 10	6,000 122	696 89	290 95

* Air cultured by bubbler samplers (9).

TABLE IV
BETA HEMOLYTIC STREPTOCOCCI EXPELLED BY CARRIERS DURING COUGHING

Carrier No.	TC	RN	LN	Saliva BHS/cc.	No. of Coughs	Droplet Nuclei BHS per cu. ft. of Air per Cough* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate per Cough Distance from Carrier, Feet		
						1½	5½	9½	1½	5½	9½
21	+++	+	+++	38,000	12	3.3	2.9	5.5	10.9	6.5	6.0
22	++	++	++	70,000	17	0	0.1	0	1.0	0.1	0
23	++	+++	+	1,080,000	12	0.1	0	0	0.2	0	0
24	++	+++	210,000	12	0	0	0.1	0	0	0
25	+++	++	+++	710,000	12	0.1	0	0	0.2	0	0
26	++	++	+++	780,000	12	0	0	0	0.2	0	0
27	+++	0	0	880,000	12	0	0	0.1	0	0	0
28	+++	0	0	780,000	12	0	0	0.1	0	0	0
29	+++	+++	0	53,000	15	0	0	0	0	0	0
30	++	++	+++	2,000	10	0	0	0	0	0	0
31	++	0	++	8,000	13	0	0	0	0	0	0
32	++	+	+	40,000	12	0	0	0	0	0	0
33	+++	+++	++	400,000	12	0	0	0	0	0	0
34	+++	0	0	160,000	15	0	0	0	0	0	0
35	+++	0	0	6,000	12	0	0	0	0	0	0
36	+++	0	0	10,000	13	0	0	0	0	0	0
37	++	0	0	360,000	12	0	0	0	0	0	0
38	+++	0	0	160,000	12	0	0	0	0	0	0
39	++	0	0	760,000	16	0	0	0	0	0	0
40	+++	+	++	200,000	14	0	0	0	0	0	0

TC = Throat culture

RN = Culture of right nostril

LN = Culture of left nostril

BHS = Beta hemolytic streptococci

* Air cultured by bubbler samplers (9)

by the activity, upon the concentration of the pathogen in the secretion and upon the mechanics and frequency of the activity. Proper understanding of the transmission of the different infections contracted via the respiratory tract must ultimately be based

TABLE V
HEMOLYTIC STREPTOCOCCI EXPELLED BY CARRIERS WHILE
COUNTING FROM 1 TO 200-400 IN FIVE MINUTES
IN A LOUD VOICE

Carrier No.	TC	RN	LN	Saliva BHS/cc.	Droplet Nuclei BHS per cu. ft. of Air* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate Distance from Carrier, Feet		
					1½	5½	9½	1½	5½	9½
26	++	++	+++	780,000	0	0	0	0	0	0
39	++	0	0	60,000	0	0	0	0	1	0
41	+++	+++	+++	31,000	0	0	0	0	0	1
42	+++	0	+	780,000	0	0	0	1	0	0
43	+++	+	+++	80,000	0	0	0	0	0	0
44	+++	+	++	0	0	0	0	0	0
45	++	0	++	230,000	0	0	0	0	0	0
46	+++	++	+++	2,800,000	0	0	0	0	0	0
47	++	+	0	54,000	0	0	0	0	0	0
48	+++	0	++	14,000	0	0	0	0	0	0

TC = Throat culture
RN = Culture of right nostril
LN = Culture of left nostril
BHS = Beta hemolytic streptococci
* Air cultured by bubbler samplers (9)

upon a knowledge of these factors as they bear upon each disease.

Let us consider sneezing and hemolytic streptococcal infection. Two separate secretions are associated with a sneeze: the fluid nasal secretion which is not propelled violently into the air and the oral secretion which is expelled at high velocity. Although most of the nasal component is discharged either in heavy masses or as fluid which must be removed with a handkerchief, a little may occasionally be atomized as droplets.¹³ The oral secretion, however, is saliva as attested by three kinds of evidence: (1) large numbers of salivary streptococci can be recovered from the air into which people have sneezed,¹⁴ (2) stroboscopic photographs indicate that the oral sneeze discharge originates in the front of the mouth¹⁰ and (3) sneeze discharges collected in empty dishes have the physical appear-

ance of saliva.* The number of group A streptococci in the saliva of carriers varies from fewer than 100 per cc. to, in exceptional instances, more than 1,000,000.¹⁵

Contrary to popular belief, sneezing usually produces very little direct pollution of the air by beta hemolytic streptococci. In the present study of twenty carriers, only one discharged large numbers of these bacteria as tiny droplet nuclei during violent un baffled sneezing although of course a carrier such as this one represents a real hazard. He possessed the two important requisites for the expulsion of large numbers of hemolytic streptococcus-containing droplet nuclei during sneezing: an unusually high contamination of the saliva (7,000,000 per cc.) and a mechanically efficient atomizing capacity.

In the case of most carriers the greatest proportion of the streptococci expelled in saliva during sneezing fall rapidly to the ground and hence do not contaminate the air until they are resuspended as dust. Sneezing, moreover, contributes relatively little to the bacterial reservoirs in dust, bedclothing and elsewhere in the environment because it is not a common symptom in carriers.†

Variability in the mechanical efficiency of sneezing among different subjects, brought out clearly by stroboscopic photographs,¹⁰ is confirmed by the patterns of expulsion of alpha (salivary) streptococci. Since the concentration of these saprophytes in the saliva is remarkably constant from person to person,‡ the number recovered from the air into which someone has sneezed is a good index of the quality of his sneezes.

Of even greater importance is the relative number of bacteria expelled in tiny droplet

* Several carriers sneezed into empty petri dishes following which the amount of saliva discharged was measured. The expulsion during one sneeze ranged from less than 0.01 to as much as 0.6 cc.

† The major contribution to these environmental reservoirs comes from the gross contamination of the hands which occurs when a nasal carrier blows his nose.¹

‡ The number of alpha streptococci per cc. of saliva varies between 7,000,000 and 40,000,000 with an average of perhaps 20,000,000. This is many times greater than the concentration of beta streptococci in saliva.

nuclei as compared with rapidly falling droplets. The fact that 35 per cent of the carriers in this series sneezed large numbers of alpha (salivary) streptococci as droplet nuclei indicates that expulsion of these tiny nuclei by sneezing is a frequent occurrence. However, it seems probable that commensal bacteria are present in only a small proportion of droplet nuclei expelled by any respiratory activity^{16,17} and that group A hemolytic streptococci are contained in a still smaller proportion. This situation may prove to be different with virus particles which because of their small size may occupy a larger proportion of droplet nuclei than do bacteria. The recent experiments of Duguid¹⁷ are interesting in this connection. He painted the inside of the mouth and fauces with congo red, then collected droplet nuclei on an oiled slide, placed in a slit sampler,¹⁸ as the nuclei were expelled during various expiratory activities. This technic enabled him to estimate the total number of nuclei expelled regardless of whether or not they contained bacteria. In a series of tests (apparently conducted with one subject) he counted from a few hundred thousand to a few million droplet nuclei after a single natural sneeze. Such studies emphasize the need for data upon the concentration of viruses in the saliva, and upon the frequency of sneezing among carriers of the virus under consideration.

Coughing does not ordinarily discharge saliva. A cough, because it originates in the back of the throat, disperses the secretions of the pharynx, the secretions of the nose if they have dripped back into the throat or material from below the larynx. This is confirmed bacteriologically by the absence of salivary streptococci from the air into which carriers coughed. The explanation of the failure of 95 per cent of carriers to expel beta streptococci by coughing, even though they were present in large numbers in the throat, is probably that the act of coughing, even volleys of twelve violent coughs, does not ordinarily shear off enough fluid from the mucous membranes of the posterior pharynx to carry significant num-

bers of these organisms. This explanation is in keeping with an observation reported by Bloomfield and Felty⁵ in 1923, that although they could collect few or no beta streptococci on blood agar plates held close to carriers' faces during coughing, they could obtain fairly large numbers from "hawking," an activity which presumably exerts a more efficient shearing action.

Previous studies have shown that carriers exhibiting positive nose cultures for hemolytic streptococci were more likely to transmit infection than those with positive throat but negative nose cultures.¹⁹ Further investigation indicated that such carriers disseminate the streptococci in highly contaminated nasal secretion which reaches the environment chiefly via the hands when the carrier blows his nose.¹ Streptococci discharged in this manner contaminate handkerchiefs, clothing, bedclothing and dust and are thrown into the air when these reservoirs are agitated. Streptococci may also be transferred by direct contact with contaminated objects in the environment or, occasionally, discharged directly into the air in droplet nuclei from the respiratory tract.

Throat carriers whose nose cultures were negative were also occasionally found to be responsible for secondary cases of streptococcal infection.¹⁹ Carrier No. 20 of this present series, who sneezed very large numbers of hemolytic streptococci, exhibited negative nose cultures at the time of the test although the nose cultures had been positive a few days before. As mentioned in the text his saliva contained an unusually high concentration of hemolytic streptococci. Such individuals, as well as some of those described in the earlier investigation of coughing and sneezing,¹ represent throat carriers who are not innocuous.

SUMMARY

1. The numbers of beta and alpha streptococci discharged into the air of an experimental room during sneezing, coughing and talking were determined in a series of forty-eight carriers of group A strepto-

cocci. By simultaneous employment of exposed blood agar plates placed upon the floor, and "broth bubbler" samplers whose intake was 3 feet from the floor, streptococci expelled in large, rapidly falling droplets could be differentiated from those discharged as droplet nuclei which remained in the air for at least several minutes.

2. The material dispersed into the air during a sneeze is chiefly saliva.

3. Four dispersion patterns of beta hemolytic streptococci by sneezing were evident. In the most common, moderate numbers were expelled in large droplets which fell rapidly to the floor 1.5 feet from the sneezer, but very few or none in droplet nuclei. In one of two less common patterns, small numbers of beta streptococci were sneezed as droplet nuclei but none in large droplets; in the other, no beta streptococci were recovered from the air. In the rarest, of which only one example was found, large numbers of beta (and alpha) streptococci were expelled both as droplet nuclei and in large droplets; many were collected as far as 9.5 feet from the sneezer. The saliva of this carrier contained huge numbers of beta streptococci.

4. Thirty-five per cent of twenty carriers sneezed out large numbers of alpha (salivary) streptococci as droplet nuclei. Eighty per cent discharged moderate or large numbers in heavy droplets which fell rapidly to the floor.

5. About one-half the streptococci expelled into the air as droplet nuclei by sneezing were still present as long as twenty minutes after the first sneeze.

6. The material expelled during coughing apparently originates in the back of the throat or below the epiglottis and contains little if any saliva.

7. Only one of twenty carriers coughed large numbers of beta streptococci into the air as droplet nuclei or in large droplets; he expelled no alpha streptococci. Ninety-five per cent of the carriers coughed few or no streptococci collected by either type of air culture.

8. Practically no streptococci were re-

covered from the air of rooms while carriers counted out loud for five minutes.

CONCLUSIONS

1. Although sneezing probably accounts for a certain number of sporadic cases of hemolytic streptococcal infection, it is not, in our opinion, important in epidemics because (1) it is not a common symptom and (2) very few sneezes discharge significant numbers of beta hemolytic streptococci into the air as droplet nuclei. The rare carriers whose sneezes heavily contaminate the air may be very dangerous if they do not baffle the sneezes efficiently. Since the material atomized in a sneeze is saliva, these individuals represent a type of dangerous carrier whose nose culture may be negative.

2. Coughing, likewise, is important only in sporadic infections for similar reasons. This symptom is more common than sneezing.

3. Talking expels negligible numbers of hemolytic streptococci.

4. Since the concentration of alpha (salivary) streptococci per cc. of saliva is remarkably constant from one individual to another, the number of these microorganisms recovered from the air in large droplets or droplet nuclei during sneezing provides a good index of the quality of sneezes.

5. A more precise understanding of the rôle of sneezing in the transmission of different respiratory diseases may result from a study of the concentration of the infective agent in the saliva and of the frequency of sneezing among carriers of the agent.

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Changes in the Bacterial Flora of the Throat and Intestinal Tract during Prolonged Oral Administration of Penicillin*

MIRIAM OLMSTEAD LIPMAN, M.D., JAMES A. COSS, JR., M.D. and RALPH H. BOOTS, M.D.
New York, New York

It is a well established fact that gram-positive micro-organisms, in general, are susceptible to the action of penicillin whereas most of the gram-negative organisms are relatively insensitive. The effect of penicillin administration on infectious agents within the body has been discussed in detail by a number of investigators. Little attention has been directed, however, toward its effect on the normal flora of the body. Likewise, the effect of prolonged administration has been studied to a limited extent only and predominantly in relation to *Streptococcus viridans* and those other organisms observed in patients with subacute bacterial endocarditis.

A clinical trial of penicillin in the treatment of arthritis¹ offered the opportunity of observing the effect of orally administered penicillin on the throat and intestinal flora of a small group of individuals over a prolonged period of time.

MATERIALS AND METHODS

Ten patients[†] with active manifestations of arthritis were selected for study. Nine of these were entirely free from respiratory tract infection at the time that the experiment was instituted. One patient (F. B.) had a nasal discharge possibly due to a chronic

[†] These patients are described in detail elsewhere.¹ Six had typical adult rheumatoid arthritis, two had rheumatoid arthritis of the spine (Marie-Strümpell spondylitis) and two had juvenile rheumatoid arthritis.

sinus infection. Three of the seven tested within one month prior to the beginning of the experiment had shown anti-streptolysin-O titers of 250 to 333 units per ml.

Amorphous penicillin (sodium salt) was used throughout the experiment. The penicillin was administered orally without buffer. Each adult received 1,000,000 units daily, in divided dosage; each child received 500,000 units daily.[‡] Duration of treatment varied from four weeks to six and one-half months. Determinations of penicillin concentration in the blood were made at frequent intervals by a serial dilution method, using *Streptococcus hemolyticus* (strain C203MV) as the test organism.

Throat and stool examinations were made, with few exceptions, prior to, at frequent intervals during and subsequent to treatment. In culturing the throats two swabs were used, both of which were first streaked on fresh, rabbit-blood agar plates; smears were prepared with one swab; the other swab was twirled in a tube of plain broth, a dilution of which was used for seeding a blood agar pour plate. A few nose and tooth cultures were made on one patient.

Each stool specimen was examined microscopically for predominant forms and was cultured on "SS" agar for enteric organisms and on blood agar, after approximately one hour's incubation in 1 per cent Na₂CO₃, for

[‡] The therapeutic regimen used is discussed in detail elsewhere.¹

* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. A preliminary report of this work was presented before the Society of American Bacteriologists, Detroit, Michigan, May, 1946.²

streptococci. In many instances, specimens were cultured anaerobically as well as aerobically.

Organisms isolated were identified roughly according to general groups. Special emphasis, however, was placed on the

growth in 6.5 per cent NaCl broth. For convenience all strains viable in blood broth after being heated at 60 to 62°C. for thirty minutes were classified as enterococci.

Most of the streptococcus and pneumococcus strains isolated, as well as many

TABLE I
PREDOMINANT THROAT FLORA PRIOR TO, DURING AND SUBSEQUENT TO PENICILLIN THERAPY

Patient	Prior to Therapy		During Therapy		Subsequent to Therapy	
	Smear (Gram Stain)	Culture	Smear (Gram Stain)	Culture	Smear (Gram Stain)	Culture
J. P.	+	Str. viridans H. hemolyticus	—	Neisseria	+	Non-hemolytic streptococci
A. G.	+	Str. viridans D. pneumoniae	—	Coliforms* M. tetragenus Str. viridans	+	Str. viridans D. pneumoniae
F. A.	+	D. pneumoniae Str. viridans	—	Coliforms Hemophilus Neisseria	+	Str. viridans D. pneumoniae
K. P.	..	Str. viridans	—	Neisseria Hemophilus	—	Neisseria Str. viridans
G. B.	+	Str. viridans D. pneumoniae	—	Coliforms	+	Str. viridans
M. W.	+	Staph. aureus Non-hemolytic streptococcus	—	Coliforms Neisseria	+	Streptococci
G. M.	+	Str. viridans	—	Coliforms† Enterococcus	+	Str. viridans
F. B.	—	D. pneumonia Str. viridans K. pneumoniae	—	Coliforms K. pneumoniae Neisseria	+	Micrococcus Staph. aureus
W. O.	..	Str. viridans	—	Neisseria Coliforms	—	Str. viridans
H. G.	+	Str. viridans D. pneumoniae	—	Str. viridans‡	+	

* Coliforms were present in all cultures, predominant on three of five occasions. M. tetragenus was predominant once, Str. viridans once.

† Coliforms were present in all cultures, predominant on five of six occasions. An enterococcus (hemolytic) predominated once.

‡ Only one examination was made after two weeks' treatment.

gram-positive cocci. All staphylococci were tested for mannitol fermentation and for coagulase production, all pneumococci for bile solubility and some for type. Cultures from all sources were examined with special reference to Str. hemolyticus. Most of the hemolytic streptococci isolated were tested for serologic grouping.³ Group A strains were tested for type. Streptococci from stool cultures and any other strains morphologically resembling enterococci were tested for heat tolerance, mannitol fermentation and

other strains, were tested by a serial dilution method⁴ for penicillin sensitivity. The sensitivity was expressed in terms of minimal concentration of penicillin required to inhibit growth of a culture diluted so as to be approximately comparable in density with C203MV, the group A hemolytic streptococcus used as standard.

RESULTS

Throat Flora. Prior to administration of penicillin, the predominance of gram-

positive cocci in all throats except one was indicated by smear or culture (Table I); in most instances results of the two examinations were consistent. *Str. viridans* predominated in the majority of cultures but each individual presented a characteristic

TABLE II
INCIDENCE OF THROAT CULTURES POSITIVE FOR HEMOLYTIC STREPTOCOCCI

Patient	Prior to Therapy	During Therapy	Subsequent to Therapy
J. P.	1 (2 strains, 1 group D and 1 unclassified*)	$\frac{0}{4}$	$\frac{1}{2}$ (untested)
A. G.	$\frac{1}{3}$ (unclassified*)	$\frac{0}{5}$	$\frac{1}{1}$ (unclassified*)
F. A.	$\frac{0}{3}$	$\frac{0}{5}$	$\frac{1}{2}$ (unclassified*)
K. P.	$\frac{1}{3}$ (group A, type 2)	$\frac{1}{10}$ (unclassified*)	$\frac{0}{3}$
G. B.	$\frac{0}{2}$	$\frac{0}{3}$	$\frac{0}{1}$
M. W.	$\frac{1}{3}$ (group A, type 38)	$\frac{0}{4}$	$\frac{2}{3}$ (group A, non-type-specific, from 1 culture, unclassified* strains from 2 cultures)
G. M.	$\frac{3}{3}$ (group F from 1, group G from 2)	$\frac{1}{6}$ (group D)	$\frac{1}{2}$ (group D)
F. B.	$\frac{0}{2}$	$\frac{0}{8}$	$\frac{0}{2}$
W. O.	$\frac{1}{1}$ (unclassified*)	$\frac{0}{10}$	$\frac{1}{5}$ (unclassified*)
H. G.	$\frac{1}{3}$ (group D)	$\frac{0}{1}$	

Numerator = number of throat cultures positive for hemolytic streptococci.

Denominator = number of throat cultures examined.

* "Unclassified" signifies negative grouping with antisera A-I inclusive.

throat picture, differing in the morphology of the predominant form or in the mixture of organisms present. Hemolytic streptococci were recovered from seven patients, group A strains from only two. (Table II). *Diplococcus pneumoniae* was recovered from five patients, type III from two, non-type-specific strains from these two and three others.

During penicillin therapy a striking change in the throat flora occurred. (Tables I and III.) Smears from all ten patients and the majority of cultures from nine indicated the predominance of gram-negative forms: saprophytic *Neisseria* (usually chromogenic), hemophilic bacteria and coliform bacteria. A culture of H. G.'s throat two

weeks after the beginning of treatment (the only examination made during her four weeks' course) presented an exception in the series, the predominance of gram-positive cocci (*Str. viridans*) and the absence of coliform bacteria.

The organisms classified as coliforms were lactose-fermenting, gram-negative rods forming grey, non-mucoid colonies unlike the watery growth of *Klebsiella pneumoniae*. In no instance were coliform colonies observed prior to the administration of penicillin. They appeared soon after the beginning of treatment, sometimes apparently in pure culture, and were observed in the majority of cultures throughout the course of therapy. (Table IV.) The pneumococci, hemolytic streptococci and hemolytic micrococci observed before treatment were absent during treatment. (Tables II, III and VI.) Strains of hemolytic streptococci different from those in the prepenicillin cultures appeared on two occasions: an enterococcus, group D, in one patient and a microaerophilic strain, which failed to group, in a second patient.

Subsequent to treatment the flora showed an increase in the variety of organisms present and became predominantly gram-positive again within a period of days or weeks. (Table I.) The change was demonstrated by smears and cultures from five patients in one week or less. Three patients were not examined until three weeks, five weeks and three months, respectively, at which times gram-positive organisms predominated in smears and cultures. The first postpenicillin throat culture on patient K. P., made three weeks after her course, showed mostly gram-negative forms; at the next examination, in six weeks, gram-positive organisms predominated in the smear and colonics of *Str. viridans* were definitely predominant in cultures. Patient H. G. had no throat examination after penicillin was discontinued.

Colonies of coliform bacteria at times appeared in postpenicillin throat cultures from seven of ten patients but were less numerous than during treatment. The time

of their disappearance varied from seven days to more than three months. (Table iv.) In the short period of observation after treatment was discontinued the incidence of pneumococci and group A hemolytic streptococci was slightly lower than before treatment. (Tables II and III.)

ment showed colonies of hemolytic *Staphylococcus aureus* only (coagulase and mannitol positive); similar staphylococci were recovered six and seven weeks after treatment.

Intestinal Flora. No definite change in the intestinal flora during the administration of penicillin was demonstrated by smears.

TABLE III
EFFECT OF PENICILLIN THERAPY ON THE PRESENCE OF VARIOUS ORGANISMS IN THE THROAT CULTURES OF TEN PATIENTS

Gram-positive Organisms				Gram-negative Organisms			
	No. of Patients Positive				No. of Patients Positive		
	Prior to Therapy	During Therapy	Subsequent to Therapy*		Prior to Therapy	During Therapy	Subsequent to Therapy*
<i>D. pneumoniae</i>	5	0	4	<i>Neisseria</i>	9	10	6
Type 3.....	2	0	0	<i>Hemophilus</i>	4	8	5
Non-type-specific...	5†	0	4†	Hemolytic.....	2	5	5
<i>Str. hemolyticus</i>	7	2	6	Non-hemolytic.	2	8	1
Group A.....	2	0	1	<i>K. pneumoniae</i>	2	2	1
Group F.....	1	0	0	<i>Coliform bacteria</i>	0	9	7
Group G.....	1	0	0				
Group D.....	2	1	1				
Group not A-L.....	3	1	4				
Group untested.....	1				
Non-hemolytic streptococci.....	10	9	9				
Viridans.....	10	6	9				
Indifferent.....	7	3	3				
<i>Staphylococcus</i>	4‡	2	3				
<i>Micrococcus</i>							
Colonies small, hemolytic.....	2	0	1				
Colonies large, grey.	6	3	8				
Diphtheroid-like organisms.....	5	4	3				

* Only nine patients were examined subsequent to treatment.

† Four prepenicillin and three postpenicillin strains included were not completely bile soluble.

‡ *Staph. aureus* was recovered from a nose culture on a fifth patient.

In one patient (K. P.) *Str. viridans* was recovered in pure culture from a tooth extracted prior to penicillin therapy. From a culture of a tooth extracted three weeks subsequent to treatment a small hemolytic micrococcus was isolated. This organism was similar morphologically, culturally and in penicillin sensitivity to strains isolated from this patient's throat cultures before and after treatment. A nose culture before treat-

Cultures of stools, however, indicated that streptococci present before treatment were somewhat inhibited during penicillin therapy. (Table v.) In eight of nine patients examined prior to and during treatment the incidence of positive cultures was lower during the latter period. Streptococci were recovered from 75 per cent of the prepenicillin cultures, from 23.2 per cent of those examined during therapy. Few speci-

mens were cultured subsequent to treatment (eight from seven patients); all, however, were positive for streptococci. Of the fifty streptococcus strains isolated from stool cultures, forty-six (92 per cent) were heat resistant. The remaining four were negative

0.05 unit to 10 units, was covered by stool strains. During treatment the organisms sensitive to less than 1 unit were recovered from only five throat cultures and from no stool cultures. Subsequent to treatment the range of sensitivity of gram-positive cocci

TABLE IV
INCIDENCE OF NON-MUCOID COLIFORM BACTERIA
IN THROAT CULTURES

Patient	Positive Cultures			First Positive Culture during Therapy (Days)	First Negative Culture Subsequent to Therapy (Weeks)
	Prior to Therapy	During Therapy	Subsequent to Therapy		
J. P.	$\frac{0}{2}$	$\frac{4}{4}$	$\frac{0}{2}$	20	3
A. G.	$\frac{0}{3}$	$\frac{5}{5}$	$\frac{1}{1}$	9	*
F. A.	$\frac{0}{3}$	$\frac{4}{5}$	$\frac{0}{2}$	23	1
K. P.	$\frac{0}{3}$	$\frac{4}{10}$	$\frac{2}{3}$	21	3
G. B.	$\frac{0}{2}$	$\frac{3}{3}$	$\frac{1}{1}$	5	*
M. W.	$\frac{0}{3}$	$\frac{4}{4}$	$\frac{2}{3}$	18	5
G. M.	$\frac{0}{3}$	$\frac{6}{6}$	$\frac{1}{2}$	5	1
F. B.	$\frac{0}{2}$	$\frac{8}{8}$	$\frac{1}{2}$	10	3
W. O.	$\frac{0}{1}$	$\frac{8}{10}$	$\frac{4}{5}$	42	11
H. G.	$\frac{0}{3}$	$\frac{0}{1}$			

Numerator = number of throat cultures positive for coliforms.
Denominator = number of throat cultures examined.
* Cultures were still positive for coliform bacteria at the time the experiment was discontinued, five weeks (A. G.) and three months (G. B.) after penicillin therapy.

to all of the enterococcus tests employed, that is, they were not viable after being heated at 60 to 62°C., they did not ferment mannitol nor grow in 6.5 per cent NaCl broth. One of these four strains grouped serologically as an H.

Penicillin therapy had no noticeable effect on the enteric bacilli or on the anaerobes of the intestinal tract.

Penicillin Sensitivity of Organisms Isolated.
Most of the gram-positive cocci isolated throughout the study were tested for sensitivity to penicillin. Strains recovered from throat cultures prior to treatment ranged in sensitivity from 0.025 unit to 10 units. Approximately the same range,

TABLE V
INCIDENCE OF STOOL CULTURES POSITIVE
FOR STREPTOCOCCI

Patient	Prior to Therapy	During Therapy	Subsequent to Therapy
J. P.	$\frac{1}{1}$	$\frac{0}{2}$	
A. G.	..	$\frac{0}{4}$	$\frac{1}{1}$
F. A.	$\frac{2}{3}$	$\frac{2}{5}$	$\frac{1}{1}$
K. P.	$\frac{2}{2}$	$\frac{2}{7}$	$\frac{1}{1}$
G. B.	$\frac{1}{2}$	$\frac{1}{3}$	
M. W.	$\frac{0}{2}$	$\frac{1}{4}$	$\frac{1}{1}$
G. M.	$\frac{2}{2}$	$\frac{3}{4}$	$\frac{1}{1}$
F. B.	$\frac{1}{1}$	$\frac{2}{7}$	$\frac{1}{1}$
W. O.	$\frac{1}{1}$	$\frac{2}{6}$	$\frac{2}{2}$
H. G.	$\frac{2}{2}$	$\frac{0}{1}$	
Total No. Patients	9	10	7
Total No. Cultures	16	43	8
Total No. Cultures Positive for Streptococcus	12	10	8
Per cent Positive for Streptococcus	75	23.2	

Numerator = number of stool cultures positive for streptococci.
Denominator = number of stool cultures examined.

from throat cultures was the same as before treatment. Stool strains isolated required from 1 to more than 10 units. (Tables vi and vii.)

Few of the gram-negative organisms isolated from either throat or stool cultures were tested for sensitivity. Of those tested, *Hemophilus hemolyticus* appeared to be

TABLE VI

PENICILLIN SENSITIVITY OF GRAM-POSITIVE COCCI FROM THROAT CULTURES

Patient	Isolation in Relation to Therapy	Organisms Tested									
		D. Pneumoniae		Str. Hemolyticus		Non-hem. Strep.		Staphylococcus			Micrococcus
		Type	Sens. u./ml.	Group	Sens. u./ml.		Sens. u./ml.	Co- agu- lase	Man- nitol	Sens. u./ml.	
J. P.	Before	Not A-L D	0.05 1.0	Viridans	0.05				
	After	Untested	0.05						
A. G.	Before	N.T.	0.025	Not A-L	1.0	Viridans	0.05	—	+	0.05	
		N.T.	0.05				0.1				
	During			Viridans	1.0				
	After	N.T.	0.05	Not A-L	0.05	Viridans	0.05				
						Indiff.	0.1				
F. A.	Before	N.T.	0.05	Viridans	0.05	—	+	1.0	
		N.T.	1.0	Viridans	0.1				
	During	Viridans (Ent.)	1.0				
	After	N.T.	0.05	Not A-L	1.0						
K. P.	Before	A, type 2	0.05	Viridans	0.05	*	Hem. 0.05
						Indiff.	1.0				
						Indiff.	10.0				
	During	Not A-L	0.025	Viridans	1.0	+	+	10.0	
						Indiff.	1.0				
	After	Viridans	0.025	+	+	10.0	Hem. 0.1
						Viridans	1.0				
G. B.	Before	3	0.1	Viridans	1.0				
M. W.	Before	A, type 38	0.025	Viridans	0.05	+	—	0.1	Hem. 0.025
						Indiff.	0.05	+	—	1.0	
	After	A (N.T.)	0.025	+	+	0.1	
				Not A-L	0.05						
G. M.	Before	F	0.05	Viridans	0.05				
				G	0.05	Viridans	0.1				
						Viridans	1.0				
	During	D	10.0	—	+	0.1	
	After	D	10.0	Viridans	0.025				
						Viridans	0.05				
						Viridans	0.1				
						Viridans	10.0				
F. B.	Before	N.T.	0.05	+	+	1.0	
	During	Viridans	0.05				
	After	Viridans	1.0	+	+	0.1	.. 0.025
W. O.	Before	Not A-L	0.05	Indiff.	0.05				
						Viridans	0.1				
	During	Indiff.	1.0				
	After	Not A-L	0.025	Viridans	0.025				
						Viridans	0.05				
H. G.	Before	3	0.1	D	0.1	Viridans	0.05				
		N.T.	0.05			Viridans	0.1				
						Indiff.	1.0				
	During	Viridans	0.1				
						Viridans	1.0				

N.T. = non-type-specific.

* = Staph. aureus, C+, M+, sensitive to 0.1 U penicillin, was recovered from a nose culture prior to therapy.

the least resistant, requiring from 1 to 10 units.

Concentration of penicillin obtained in the blood of these patients is discussed in detail elsewhere.¹ Peak levels varied from 0.1 unit (in J. P.) to 1.6 unit (in G. M.).

In the series of individuals described in the present report the bacterial flora of the throat prior to treatment was normal. Gram-positive organisms were predominant throughout (except in some cultures from a patient with chronic sinusitis), and those

TABLE VII
PENICILLIN SENSITIVITY OF STREPTOCOCCI FROM STOOL CULTURES

Patient	Prior to Therapy						During Therapy						Subsequent to Therapy					
	Resistance to 60-62°c.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity	Resistance to 60-62°c.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity	Resistance to 60-62°c.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity
						u./ml.						u./ml.						u./ml.
J. P.	- +	- +	- +	- +	H D	0.1 1.0												
A. G.	+ +	+ -	+ +	- +	D D	>10.0 10.0
F. A.	+ + +	- - -	- - - D	0.05 1.0 10.0	+	-	+	+	10.0	+ + +	- + +	+ + +	+ + +	D D D	10.0 10.0 10.0
K. P.	+ +	- -	- +	+ ..	O D	10.0 10.0	+ ..	- ..	+ ..	+	10.0	+ ..	- ..	- ..	-	10.0
G. B.	+	-	-	-	..	0.1												
M. W.	- +	- -	- +	- -	O D	1.0 10.0
G. M.	- + + + +	+ - - - -	- - - + +	.. - - - -	O	0.05 0.05 0.1 0.05 0.1	+ + + +	+ + - +	+ + + +	- + + +	D D	10.0 10.0 10.0 10.0	+ + + +	+ + +	+ +	- -	D D D D	10.0 10.0 10.0 10.0
F. B.	+	-	+	+	O	10.0	+	-	+	+	..	10.0	+	-	+	+	D	10.0
W. O.	+	-	-	+	D	10.0	+	-	+	+	D	10.0	+	-	+	+	D	>10.0
H. G.	+	-	+	10.0												

0 = No reaction with antisera of groups A to L, inclusive.

COMMENTS

Elimination of gram-positive pathogens from the throat during oral administration of penicillin has been reported by Keith et al.,⁵ by Levitt and Leathen⁶ and by others. No reports on the effect of penicillin administered orally over prolonged periods of time have come to our attention.

tested were, with one exception, sensitive to 1 unit or less of penicillin per ml. The shift from a predominantly gram-positive to gram-negative flora during penicillin therapy was striking. The significance of such a change and its possible effect upon the susceptibility of the individual to various infections remains to be determined.

Difference in the incidence of streptococcus-positive cultures prior to and during treatment seems significant although the inaccuracy of a comparative study of such material is recognized. Whereas 75 per cent of stool cultures prior to penicillin therapy were positive for streptococci, only 23 per cent were positive during therapy. The streptococcus strains isolated during treatment showed a relatively low sensitivity to penicillin.

The possible development of bacterial resistance to penicillin on low dosage or on prolonged administration of penicillin has been discussed at length by many investigators. The present study has offered opportunity to observe the effect of prolonged administration of penicillin in this connection. Comparison of similar strains recovered from throat or stool cultures before and after penicillin therapy revealed no definite evidence of an increase in resistance to the drug. All strains of pneumococci, hemolytic micrococci and hemolytic streptococci isolated from throat cultures subsequent to penicillin therapy were as sensitive as strains with similar characteristics isolated prior to treatment. Two patients showed slightly more resistant strains of *Str. viridans* and one patient a slightly more resistant strain of *Staph. aureus* after completion of the course of therapy than before treatment. However, no proof of the identity of these strains exists.

Continuous absence of gram-positive organisms, particularly streptococci, from the throat flora during prolonged penicillin administration and the apparent failure of the streptococci to acquire penicillin resistance, is of interest in connection with the problem of the prophylaxis of rheumatic fever by means of anti-streptococcal agents.

SUMMARY

A bacteriologic study of the throat and intestinal flora of ten patients with arthritis, treated orally with 500,000 to 1,000,000 units of penicillin daily over a prolonged period of time, has been carried out.

Upon administration of penicillin there was a sudden change in the bacterial flora of the throat from gram-positive to gram-negative. Coliform bacteria appeared in the throat early in the course of treatment and were present, and often predominant, throughout the course. Subsequent to treatment there was a rapid reappearance of gram-positive cocci in the throat. The coliform organisms disappeared gradually.

There was a lower incidence of streptococcus-positive stool cultures during, than prior to or subsequent to penicillin therapy.

No difference in the range of penicillin sensitivity of the gram-positive cocci isolated from throat cultures prior to and subsequent to treatment was demonstrated. Penicillin-sensitive organisms were infrequent in the throat and stool cultures during treatment.

There was no evidence that bacterial resistance to penicillin developed during the course of therapy.

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Prolonged Administration of Penicillin in Arthritis*

JAMES A. COSS, JR., M.D., ELI BAUMAN, M.D., RALPH H. BOOTS, M.D.
and MIRIAM OLMSTEAD LIPMAN

New York, New York

PREVIOUS studies of the effect of penicillin† in the rheumatic group of diseases have not been encouraging.¹⁻³ However, it has been reported that in other conditions due to known bacterial agents failures in treatment have often been linked with failure to use adequate dosage of penicillin or to continue treatment for a long enough time.^{4,5} The use of penicillin in rheumatoid arthritis is suggested by the hypothesis that this disease may be due to infection with a penicillin-sensitive organism. The hemolytic streptococcus, Group A, has been implicated on immunologic grounds because a positive streptococcus agglutination reaction occurs in the majority of patients with rheumatoid arthritis.⁶ However, the specificity of the reaction has not been established.⁷ This evidence has been supported to a slight extent by the demonstration, in agglutinating sera, of precipitins for fractions of *Streptococcus hemolyticus*⁸ and by an elevation in the antistreptolysin-O titer of sera from many early cases of rheumatoid arthritis.⁹ If any infectious agent is to receive consideration in etiology, most evidence points toward this organism.^{10,11}

Some workers have suggested that rheumatoid arthritis may be due not to just one invasion of a bacterial agent but to repeated infections. If this were true, prolonged administration of an antibacterial agent might be effective when treatment over a

short period of time had previously failed. Because of the low incidence of upper respiratory infection and rheumatic diseases in tropical and subtropical regions,¹² it was thought that eliminating or minimizing the respiratory infections these patients so commonly harbor might exert a favorable influence on the course of their illness.

Our purpose has been primarily to determine whether prolonged oral administration of penicillin would alter the course of arthritis; second, to see if the incidence or severity of various upper respiratory infections usually associated with exacerbation of arthritis could be diminished; third, to determine the levels of penicillin obtainable by the oral route and finally to observe what phenomena, if any, might result from large doses of penicillin given over a long period of time.

MATERIALS AND METHODS

Ten patients were selected for treatment. The study was limited to patients with active disease who were capable of following directions and keeping personal records, in whom the diagnosis was definite and who had received little or no other treatment. Six patients had adult rheumatoid arthritis, Two had rheumatoid spondylitis (Marie-Strümpell) and two patients had juvenile rheumatoid arthritis. Each patient was given a daily record sheet on which he recorded the time that penicillin was taken, the amount, any change in symptoms, the occurrence of any illness or infection and any reaction to penicillin.

† We are indebted to Mr. John L. Smith of Charles Pfizer & Company of Brooklyn, for the supply of penicillin.

* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Penicillin (sodium salt) was dispensed in plain, gelatin capsules without buffer, made up so that six capsules equalled 1,000,000 units for the adults and six capsules equalled 500,000 units for the two children. The patient was instructed to empty the contents of one capsule six times a day into 4 to 6 ounces of tap water which was ingested immediately without buffer or antacid. Each of the adults received 1,000,000 units of penicillin daily. One child, K. P., was unable to tolerate the penicillin solution so she was given the unopened gelatin capsule with tap water. For the first two weeks she received 1,000,000 units daily, then this was reduced to 500,000 because the larger amount caused nausea. The other child, F. A., disliked the taste of the aqueous solution so the contents of each capsule were given in 4 ounces of milk, maintaining a daily dose of 500,000 units. No buffering agent, enteric coating or antacid was employed with the drug. It is necessary to give four or five times the intravenous or intramuscular dose of penicillin orally to obtain comparable blood levels.¹³⁻¹⁵ For this reason we gave the large amounts recorded.

Many laboratory procedures were carried out including the agglutination test for hemolytic streptococcus,⁶ antistreptolysin-O determinations,¹⁶ blood counts, urinalysis and repeated erythrocyte sedimentation rates.¹⁷ The concentration of penicillin in the blood and the penicillin-sensitivity of organisms isolated from stool and throat cultures were determined by the serial dilution method.^{18,19} Stool and throat cultures were taken before, during and following the course of penicillin. Tongue scrapings of patients developing a brown tongue were examined by Dr. Rhoda Benham in the mycology laboratory. Gastric expressions were done to rule out the possibility of gastric anacidity. This was not found in any instance.

Of ten patients, one failed to continue treatment after four weeks. The remainder completed courses of three to six months. The average total amount of penicillin

administered to each patient during the course of treatment was 127,900,000 units. This would seem to be an adequate trial of therapy.

RESULTS

Our criteria of clinical improvement were the same as used in previous communications from this clinic,²¹ namely, (1) *striking improvement*—marked subjective and objective change in the patient accompanied by a convincing drop in the sedimentation rate. It will be noted that only one patient showed such a response (F. A.) and he has juvenile arthritis of the type in which we have learned to expect a better than average prognosis; (2) *moderate improvement*—a significant change in the patient's condition subjectively and objectively accompanied by a convincing fall in sedimentation rate; (3) *slight improvement*—improvement difficult to define, drop in sedimentation rate; (4) *none*.

The degree of clinical improvement is noted in Table I. When the results in this study are compared with reports of other measures,^{22,23} they are not encouraging. (Table I.) A drop in erythrocyte sedimentation rate to normal occurred in only two patients. Only one of these has maintained a low rate during the follow-up period. A definite drop in sedimentation rate occurred in three patients, little change or an actual rise in rate occurred in the five remaining subjects.

There was an apparent decrease in incidence and severity of upper respiratory infections during the course of penicillin therapy but no correlation could be established between the degree of improvement and presence or absence of such infections. Upper respiratory infections of less than one week's duration without systemic effect have been considered mild; those accompanied by a low-grade fever or lasting more than a week have been considered moderate to severe.

In Table II the range of levels of penicillin in units per milliliter and median values is shown. (In the eighth case, penicillin was

administered in gelatin capsules rather than aqueous solution.) Adequate levels have been obtained comparable to those reported with intramuscular or intravenous administration. Our peak levels have been from 0.1 to 1.6 u/ml. These were attained using

tongue serapings of six patients were examined by Dr. Rhoda Benham and a monilia was cultured from four of them. Two cultures were identified as *Monilia albicans*, two others were non-pathogenic monilia. After the brown pigmentation was

TABLE I
RESULTS OF TREATMENT OF ARTHRITIS WITH ORAL PENICILLIN

Patient	Diagnosis	Duration of Treatment	Incidence of Upper Respiratory Infections	Median Erythrocyte Sedimentation Rate			Improvement
				Before	During	After	
J. P.	Marie-Strümpell spondylitis	14 wk.	mild × 1	44	34	47	slight
A. G.	Marie-Strümpell spondylitis	26 wk.	none	60	58	57	none
F. A.	Juvenile rheumatoid arthritis	28 wk.	mild × 1	44	11	10	striking
K. P.	Juvenile rheumatoid arthritis	26 wk.	moderate × 1 mild × 1	104	82	63	slight
G. B.	Adult rheumatoid arthritis	12 wk.	mild × 1	32	18	52	moderate
M. W.	Adult rheumatoid arthritis	22 wk.	none	41	31	47	slight
G. M.	Adult rheumatoid arthritis	27 wk.	none	92	90	62	none
F. B.	Adult rheumatoid arthritis	28 wk.	mild × 1 rhinorrhea × 2	62	59	80	none
W. O.	Adult rheumatoid arthritis	28 wk.	none	54	43	30	slight
H. G.	Adult rheumatoid arthritis	4 wk.	none	42	33	61	none

an aqueous unbuffered solution of penicillin without any protective agent such as an antacid or enteric coating and seem to corroborate the recently published suggestion that gastric acidity is of minor importance in the destruction of orally administered penicillin.^{13,14,25,26}

Various reports of toxic reactions to penicillin have appeared.²⁷⁻³⁵ In our series nausea occurred in three patients, it subsided spontaneously in two while treatment was continued and in the third patient, a 60 pound child, it subsided when the dose was reduced from 1,000,000 to 500,000 units daily. Transient diarrhea was noted in four patients and a small localized rash of two days' duration occurred in another. It was not necessary to discontinue treatment in any instance.

An unexpected finding was the appearance of a brown discoloration of the tongues in seven patients. In some instances a furry appearance accompanied the brown color, suggesting the presence of a fungus. The

definite, two patients were told to swallow the capsules intact rather than in solution. In five to ten days the brown color was nearly gone. One patient, a heavy smoker, retained a tinge of brown presumably because of tobacco. All other patients exhibiting a brown tongue showed a disappearance of pigmentation as soon as treatment was stopped. The color induced was probably due to a concentration of colored material from the penicillin used.

The bacteriologic results of this study, a preliminary survey of which has been presented, are being reported in detail elsewhere.³⁷ Before treatment the predominance of gram-positive organisms in the throats of all patients except one was indicated by smears and cultures. In most instances colonies of *Streptococcus viridans* were predominant. Other gram-positive organisms appeared intermittently in some patients prior to therapy. During penicillin therapy throat smears and cultures indicated a predominance of gram-negative forms similar to

those observed occasionally in pre-penicillin cultures, and coliform bacteria which appeared first a short time after beginning therapy. Penicillin-sensitive organisms, including pneumococci and hemolytic streptococci, group A, disappeared from the

streptolysin-0 or streptococcus agglutination titers following penicillin therapy.

COMMENTS

In studying the results with penicillin therapy it should be borne in mind that from 50 to 70 per cent of arthritics will exhibit some degree of improvement with only general supportive treatment.²⁰ Using various empirical remedies even better results are reported, and in recent years many observers have believed that chrysotherapy was of definite benefit in a large percentage of cases.³⁸ Aside from the effects on arthritis, there was a diminution in severity and frequency of upper respiratory infections noticed by all of the patients. These infections may vary so much from year to year in any one patient, however, that it would be difficult to assign great importance to this observation.

Penicillin levels of 0.05 u/ml. are effective against most pneumococci, streptococci and other oral pathogens, but not against organisms requiring more than 0.05 unit for inhibition of growth *in vitro*. One report has suggested that effective blood levels during the usual intramuscular doses range from 0.02 to 0.16 u/ml.²⁴ Peak levels obtained in this work were usually much higher than this. Usually higher levels with a given dose of penicillin are obtained if the drug is taken more than one-half hour before²⁵ or two hours after meals. With such a schedule only minor variations from the median should appear. Actually, it is impossible to control the exact time of administration in ambulatory patients so that the fluctuations have occasionally been greater as noted in Table II.

A striking observation, considering the length of time and large amounts of penicillin involved in this study, was the paucity of toxic reactions. Mild reactions did occur but it was never necessary to stop treatment because of them. In fact all of the various reactions listed previously disappeared in a day or so as treatment continued.

In a study of one hundred normal throat cultures Dr. Benham isolated *M. albicans*

TABLE II
PENICILLIN CONCENTRATION IN SERUM OF TEN PATIENTS
RECEIVING 500,000 TO 1,000,000 UNITS DAILY
IN AQUEOUS SOLUTION

Case	Single Dose ¹ (Units)	Interval between Dose and Bleeding	Unit Penicillin per ml Serum	
			Range	Median
F. A.	83,000	30 min.	0.05 - 0.4	0.2
		1 hr.	0.0125 - 0.2	0.2
		2 hr.	<0.0125 - 0.0125	<0.0125
		3 hr.	<0.0125 - <0.0125	<0.0025
G. B.	166,000	30 min.	0.05 - 0.4	0.2
		1 hr.	0.1 - 0.2	0.15
		2 hr.	0.025 - 0.025	0.025
		3 hr.	<0.0125 - 0.025	<0.025
F. B.	166,000	30 min.	0.2 - 0.4	0.2
		1 hr.	0.05 - 0.4	0.2
		2 hr.	0.0125 - 0.05	0.05
		3 hr.	0.0125 - 0.025	0.025
H. G.	166,000	30 min.	0.4	0.4
		1 hr.	0.1 - 0.1	0.1
		2 hr.	0.0125 -	0.0125
		3 hr.	<0.0125	<0.0125
A. G.	166,000	30 min.	<0.0125 - 0.2	<0.0125
		1 hr.	<0.0125 - 0.1	0.0125
		2 hr.	<0.0125 - 0.05	<0.0125
		3 hr.	<0.0125 - 0.0125	<0.0125
G. M.	166,000	30 min.	<0.0125 - 1.6	0.6
		1 hr.	<0.0125 - 0.8	0.4
		2 hr.	<0.0125 - 0.05	<0.0125
		3 hr.	<0.0125 - 0.025	<0.0125
W. O.	166,000	30 min.	0.1 - 0.8	0.4
		1 hr.	0.025 - 0.8	0.2
		2 hr.	0.05 - 0.4	0.1
		3 hr.	0.025 - 0.2	0.05
K. P.	83,000	30 min.	0.2 - 0.8	0.8
		1 hr.	0.05 - 0.2	0.1
		2 hr.	<0.05 - 0.05	0.025
		3 hr.	<0.05 - 0.025	<0.0125
J. P.	166,000	30 min.	<0.0125 - 0.1	0.025
		1 hr.	<0.0125 - 0.1	0.0125
		2 hr.	<0.0125 - 0.025	<0.0125
		3 hr.	<0.0125 - 0.0125	<0.0125
M. W.	166,000	30 min.	<0.0125 - 0.4	0.05
		1 hr.	<0.0125 - 0.1	0.05
		2 hr.	<0.0125 - 0.025	<0.0125
		3 hr.	<0.0125 - 0.0125	<0.0125

¹ This dose was repeated six times daily.

throats. Examination of stool specimens has indicated a definite inhibitory effect on the gram-positive diplococci of the intestinal tract.

No effect was observed on the anti-

from 18 per cent,³⁶ thus it is impossible to draw conclusions from our small series. No correlation has been established between this phenomenon and penicillin levels but it was observed that patient A. G., who has seldom had high levels when tested, developed a brown, shaggy tongue on the fifth day of treatment, earlier than any other patient.

SUMMARY AND CONCLUSIONS

1. Penicillin has been given by the oral route to ten patients with arthritis. Two patients were moderately to markedly improved, four patients were slightly improved and four patients were unimproved during the course of this study.

2. There seemed to be a diminution in incidence and severity of upper respiratory infections.

3. With one exception, therapeutic levels of penicillin were attained in the serum by oral administration even though no antacid, buffer, enteric coating or other protection was employed.

4. Transient reactions consisting of nausea or diarrhea were observed in five instances. One patient had a two-day rash localized to one leg, probably not associated with penicillin. In no case was it necessary to stop treatment because of persisting reactions.

5. Seven patients developed a brownish discoloration of the tongue while receiving penicillin. Fungus cultures were obtained from six patients, two were positive for *M. albicans*, two had non-pathogenic monilia and two were negative.

6. Oral penicillin was effective against susceptible organisms when the dosage was increased to four or five times the usual intramuscular dose.

7. Bacteriologic studies demonstrated a change in the predominant organisms of the throat from gram-positive to gram-negative, the disappearance from the throat of penicillin-sensitive organisms, the appearance of coliform bacteria in the throat and a decrease in the prevalence of gram-positive diplococci in the intestinal tract.

8. Antistreptolysin and streptococcus agglutination titers were unchanged with penicillin therapy.

9. Penicillin is not recommended for the treatment of rheumatoid arthritis.

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Oral Penicillin in the Treatment of Various Bacterial Infections^{*}

JAY A. ROBINSON, M.D., HAROLD L. HIRSH, M.D. and HARRY F. DOWLING, M.D.

Washington, D. C.

ORAL administration of a drug is the method of choice from the standpoint of the patient's comfort and physician's convenience. In the early studies of the absorption of small doses of penicillin from the gastrointestinal tract only low concentrations were demonstrated in the serum although higher concentrations were obtained in patients with achlorhydria.^{1,2} From these observations, plus the fact that penicillin was destroyed in an acid medium, the hypothesis was entertained that low serum levels following oral administration were the result of destruction by gastric juice.¹⁻⁴ Many investigators combined penicillin with various protectives in an effort to decrease this destructive action.^{3a,26} Further studies of the absorption of large doses of penicillin in aqueous solution given orally demonstrated that the serum concentrations were as good as those obtained with the use of protectives.^{2,27} These variable results stimulated several investigators to review the problem of oral administration of penicillin.

McDermott and his collaborators²⁸ found that at a pH of 2 penicillin was destroyed rapidly and completely; at pH 4 the destruction was slow and incomplete and at pH 7.2 to 7.5 no destruction occurred. They further demonstrated that in normal subjects the pH of the gastric juice was frequently 4 or above, and concluded that the destruction of penicillin in the stomach accounted for only a small fraction (10 to 15 per cent) of the ingested dose. Free and his associates²⁹ also found that if large doses were given orally, most of the penicillin

escaped the action of the gastric juice and that the amount available for absorption through the duodenum was sufficient to produce significant serum concentrations.

Several investigators^{28,30,31} recently studied the absorption and destruction of penicillin in various parts of the gastrointestinal tract. They found that the maximal amount of penicillin absorbed from the duodenum was approximately one-third of the amount present, and that destruction of the drug did not occur. Their explanation for the fact that only small amounts were absorbed was that passage through this organ was too rapid to permit complete absorption.

Approximately one-fifth of the amount which reached the jejunum and ileum was absorbed while nearly one-half of the penicillin present in this region was destroyed. Of the amount which reached the colon, only 5 per cent was absorbed while about four-fifths was destroyed. These investigators believed that the destruction in the intestinal tract was due mainly to penicillinase produced by some of the bacteria. An average of 2 per cent of the ingested dose was excreted in the feces. These data indicated that the relative inefficiency of oral dosage was due to the incomplete absorption in the upper intestinal tract and destruction in the lower portions. Furthermore, the effect of protective substances was negligible in comparison with the other factors involved.

In view of the fact that oral administration of penicillin is followed by therapeutically effective concentrations of the antibiotic

^{*} From the George Washington University and Georgetown University Medical Divisions, Gallinger Municipal Hospital, and the Departments of Medicine, George Washington University School of Medicine and Georgetown University School of Medicine, Washington, D. C.

in the serum when sufficiently large doses are given, we decided to employ this route in the treatment of certain diseases.* In general, we selected a dose five times as high as that which we were accustomed to

TABLE I
RESULTS OF ORAL PENICILLIN THERAPY IN VARIOUS INFECTIONS

Disease	Recovered	Unimproved	Died	Dosage-Schedule
Pneumococcal pneumonia.....	109	...	4	75,000 units every 3 hr. until afebrile for 48 to 72 hr.
Scarlet fever.....	94	..	0	125,000 units every 3 hr. for 5 days
Tonsillitis and pharyngitis.....	38	0	..	100,000 to 125,000 units every 3 hr. for 5 days
Erysipelas.....	6	..	0	100,000 to 125,000 units every 3 hr. for 5 days
Otitis media.....	16	1	..	100,000 to 125,000 units every 3 hr. for 48 hr. after all evidence of active infection have disappeared
Vincent's angina.....	6	0	..	50,000 to 75,000 units every 2 to 3 hr. for 3 to 4 days
Infections of the skin...	21	1	..	125,000 units every 3 hr. for 5 days
Bacterial endocarditis	0	2	..	Oral penicillin not recommended
Total.....	290	4	4	

administer intramuscularly for the same diseases.

RESULTS

The dosage schedules and the results of treatment in 298 patients with various infections treated with oral penicillin are listed in Table I.

Pneumococcal Pneumonia. Included in the series are 113 patients with pneumonia. No selection was practiced. All patients diagnosed as having pneumonia during the times when oral preparations were available were treated by the oral route. Sputum specimens and blood cultures were obtained before therapy was begun. As shown in Table II a pneumococcus was typed from the sputum of ninety-one patients. In the

*The penicillin used was in the form of tablets buffered with calcium carbonate and was supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.

twenty-two patients in whom a pneumococcus was not found the presumptive diagnosis of pneumococcal pneumonia was made on the basis of a typical history, characteristic physical and x-ray findings

TABLE II
PATIENTS WITH PNEUMONIA—ARRANGED ACCORDING TO PNEUMOCOCCUS TYPES

Type of Pneumococcus	All Cases		Bacteremic Cases	
	No.	Died	No.	Died
1	10	1	2	1
2	12	0	1	0
3	11	0	0	0
4	6	0	2	0
5	1	0	0	0
6	5	0	0	0
7	13	1	2	0
8	6	0	1	0
Other types	27	1	1	1
No type obtained	22	1	0	0
Total	113	4 (3.5%)	9	2 (22%)

and leukocytosis. Nine patients had positive blood cultures. Forty-four (39 per cent) of the patients were over forty years of age. (Table III). Lobar pneumonia was diagnosed in ninety-eight patients and broncho-

TABLE III
PATIENTS WITH PNEUMONIA—ARRANGED ACCORDING TO AGE

Age Group	No.	Died
12-20	10	0
21-30	26	0
31-40	33	2
41-50	20	0
51-60	12	1
61-70	7	0
over 70	5	1
Total	113	4

pneumonia in fifteen. Twenty patients had involvement of more than one lobe. Among the eighty-eight patients for whom the day of onset could be definitely established, penicillin treatment was begun on the first two days of the disease in 39 per cent of

cases; on the third or fourth days in 31 per cent; on the fifth to the seventh days, inclusive, in 25 per cent and after the seventh day in 5 per cent. None of the patients had received sulfonamides or antibiotics before admission to the hospital.

The dose of penicillin employed in most instances was 75,000 units every three hours, day and night, until the patient's temperature fell and remained below 100°F. for forty-eight to seventy-two hours. Fifteen patients were given 80,000 units and two received 100,000 units every three hours. The larger doses were given without regard to the severity of the disease but because preparations of penicillin were available which made such a dosage regimen convenient.

The results of oral penicillin therapy were comparable with those obtained by intramuscular doses approximately one-fifth as great.

Some of the cases reported herein were included in a previous study^{5b} which showed that the case fatality rates, the speed of temperature fall and incidence of complications were comparable with the results in patients treated by the oral and by the intramuscular route, providing the oral dose was five times as great as the intramuscular.

Death occurred in four (3.5 per cent) of the 113 patients in whom oral treatment was employed. Two of the patients were in the age group of thirty-one to forty years. Both had overwhelming infections accompanied by bacteremia and were moribund on admission. One was admitted on the fifth day of illness and the other on the seventh day. Both patients died soon after treatment was started, one patient eight hours and the other fifteen hours after the first dose of penicillin.

The patient aged fifty-four who died was admitted to the hospital on the seventh day of his illness. He died thirty-nine hours after treatment was started and at autopsy was found to have bronchopneumonia throughout the right lung and in the left lower lobe and a fibrinous pericarditis.

The fourth fatality occurred in a ninety-

eight year old colored female who recovered from pneumonia and died ten days later from a hemorrhage of the intestinal tract, the cause of which was unknown. Autopsy was not obtained.

Our results with oral penicillin were similar to those obtained by others,^{20,21,32} some of whom employed smaller, and others larger doses.

Infections Caused by Beta Hemolytic Streptococci. The pronounced susceptibility of the beta hemolytic streptococcus to the bactericidal action of penicillin stimulated us to treat scarlet fever with this antibiotic. We have given penicillin orally in doses of 125,000 units every three hours for five days to thirty patients, and 100,000 units every four hours for the same period of time to sixty-four patients. The results with oral administration in these doses were comparable to those obtained in eighty-six patients treated by parenteral injections of 25,000 units every three hours for five days.³³ The penicillin caused a prompt fall in temperature, a decrease in toxicity and a pronounced reduction in the incidence of pyogenic complications and the carrier state. Furthermore, in all patients from whose throat a hemolytic streptococcus was cultured, the causative organism disappeared within forty-eight hours and did not reappear while the patient was under observation. The need for antitoxin is apparently obviated except in severely toxic patients or in those who show no response to penicillin after an adequate trial for forty-eight to seventy-two hours. Since penicillin therapy decreases the number and severity of complications, we believe that even the patients with mild cases should have the benefit of the antibiotic. On admission several patients had pyogenic complications such as otitis media, sinusitis and infected wounds. All of these complications responded promptly to penicillin therapy. A more detailed report on the treatment of scarlet fever with penicillin has been published elsewhere.³³

Patients with streptococcal infections of the pharynx without rash, treated with peni-

cillin orally in doses of 100,000 units to 125,000 units every three or four hours for five days, responded as well as those with scarlet fever. Hemolytic streptococci disappeared promptly from the throat cultures and the symptoms regressed rapidly. The patients appeared well in about seventy-two hours. The results in these thirty-eight patients are comparable to those obtained in thirty patients treated by us with parenteral penicillin.³⁴ Penicillin treatment should be continued for a minimum of five days; otherwise the incidence of complications and recurrence is high and the complications may be severe.³⁵ Others have reported similar results.^{32,36}

Although the sulfonamides have been highly effective in the treatment of erysipelas, we believe that penicillin is the drug of choice. The six patients treated with 125,000 units of penicillin orally every three hours recovered in five days although the amount of skin involved covered as much as three-fourths of the face in some instances. Within twenty-four hours of the beginning of therapy the lesion stopped spreading. Thereafter, there was prompt regression of all symptoms as well as of the area of involvement so that within an average of five days the skin appeared essentially normal. These results were similar to those obtained in four patients whom we treated parenterally.³⁴

Acute Otitis Media. The micro-organisms which affect the middle ear are usually amenable to penicillin therapy. We have treated seventeen such infections with oral penicillin. The results were similar to those observed in fifteen patients treated with penicillin parenterally.³⁴ The dosage schedule employed was 100,000 to 125,000 units every three hours and this was continued for forty-eight hours after all evidence of active infection had disappeared. Ten patients had acute catarrhal otitis media and seven had a suppurative process. Cultures of the pus in the latter patients yielded beta hemolytic streptococcus in five cases, Staphylococcus aureus in one case and pneumococcus, Type III, in another case. In nine

patients the otitis media was apparently a primary infection while in seven patients the ear involvement followed an acute upper respiratory infection. One patient also had Type III pneumococcal pneumonia. Not included in the tabulations are an additional seven patients with scarlet fever who had catarrhal otitis media which was present on admission and which responded to the penicillin administered for the scarlet fever. The patients with acute catarrhal otitis media showed regression of the abnormal findings within twenty-four hours. All signs were usually gone by the third or fourth day. In all of the patients with suppurative otitis media the drainage became thinner and less in amount within twenty-four hours and stopped completely within seventy-two hours. Regardless of the kind of pathologic condition present, the treatment was continued for forty-eight hours after all evidence of active infection had disappeared. Average duration of treatment was seven days. Myringotomy was avoided in all patients except one who had an acute catarrhal otitis media. In this patient the myringotomy was performed after the patient had made a favorable response and the operation may not have been necessary. The one patient who failed to respond had an acute catarrhal otitis media. After there was no improvement following seventy-two hours of oral penicillin therapy the patient was given 25,000 units of aqueous penicillin intramuscularly every three hours for five days with only slight improvement. Recovery finally occurred after seven days of sulfadiazine therapy. Gyorgy and his associates³² and Lierle and his co-workers³⁶ have reported results similar to ours with the use of oral penicillin in the treatment of otitis media.

Vincent's Stomatitis and Pharyngitis. The effectiveness of penicillin in Vincent's stomatitis and pharyngitis has been demonstrated whether the antibiotic is administered orally,³⁶ parenterally^{37,43,44} or is employed locally.^{38,43,45,48} Our results with oral penicillin in the treatment of six patients with Vincent's stomatitis and pharyngitis were

excellent. Doses of 50,000 to 75,000 units were given every two to three hours for three to four days. Vincent's organisms disappeared within twenty-four hours after the start of therapy, and the symptoms subsided and the lesions disappeared within several days. Although the results with oral therapy were as good as those obtained in six patients treated with intramuscular injections,³⁴ treatment by the latter method has the advantage that 15,000 to 25,000 units given intramuscularly every three hours for one day will control most infections and only a few patients will require two to four days of treatment.

Infections of the Skin and Subcutaneous Tissues. Prompt recovery occurred in twenty-one of twenty-two patients with various infections of the skin and subcutaneous tissues, including abscesses, cellulitis, carbuncles and impetigo. These patients were given 125,000 units orally every three hours for five days. In all instances the lesions showed evidence of prompt regression with complete resolution of the infections by the time therapy was discontinued. Others have reported similar experiences.^{20,32} Our results were comparable to those which we obtained in nineteen patients to whom we³⁴ gave penicillin parenterally. The one failure occurred in a patient who developed an abscess following an injection of protamine zinc insulin. Healing did not occur until incision and drainage were performed. The pus at that time was cultured and was found to be sterile.

Bacterial Endocarditis. Treatment with parenteral penicillin has revolutionized the prognosis of bacterial endocarditis. Successful use of oral penicillin in the treatment of this infection has been reported.⁴⁹ We started treatment of two patients with the administration of penicillin by mouth in doses of 100,000 to 200,000 units every three hours. When there was no clinical improvement and the blood cultures continued to be positive after two days of oral penicillin, intramuscular therapy was substituted. This was followed by prompt control of the infection. In the case of one

patient the sensitivity of the *Streptococcus viridans* was found to be 0.039 units of penicillin/cc. The concentration of penicillin in the serum was determined at regular intervals and frequently found to be below the desired level for the causative organism. Inasmuch as bacterial endocarditis is a serious disease in which penicillin therapy may sometimes fail even under what appear to be the most favorable circumstances and since parenteral therapy in our hands⁵⁰ as well as elsewhere now results in cures in about 75 per cent of these patients, we believe that oral therapy should not be employed.

Gonorrhea. We have not treated any patients with gonorrhea by the oral route. Meads and Finland⁵¹ reviewed the cases of 225 patients given oral penicillin. They reported that a favorable response occurred in 190 (85 per cent) of the patients. The dose of penicillin ranged from 100,000 to 1,600,000 units given over a period of one to sixty-nine hours. They concluded that in order to achieve results comparable with those obtained with 75,000 units or more intramuscularly, it is probably necessary to use a total oral dose of 600,000 units or more. Others⁵² have had similar results with 600,000 units over a period of seven hours. One investigator⁵³ reported cures in 92.7 per cent of his patients using 200,000 units given twice over an eight-hour interval.

TOXIC REACTIONS

A number of patients with other diseases were given oral penicillin, making a total of 350 patients who were treated by this route. Among these, eight had toxic reactions. One patient was given two courses of oral penicillin and developed nausea and vomiting immediately after taking each dose of the first course. She had no reaction during the second course. Six patients complained of mild diarrhea which was present only during penicillin therapy and which did not interfere with treatment. No other cause for the diarrhea was found. The eighth patient developed urticaria and pruritus on the third day of treatment. She

was also receiving aspirin and codeine sulfate. The symptoms were relieved by benadryl given orally. Treatment with penicillin was continued for an additional two days. After the completion of therapy she was given test doses of aspirin, codeine sulfate and penicillin without developing a reaction to any of them.

It is quite likely that the nausea, vomiting and diarrhea were due to mechanical factors from the number of tablets that were taken rather than to hypersensitivity to penicillin. When allergic manifestations alone are considered, the incidence of toxic reactions due to oral penicillin is much less than that observed by us in patients treated with the antibiotic given parenterally. Urticaria or fever developed in seven of the 600 patients to whom we gave penicillin intramuscularly or intravenously.

COMMENTS

Simplicity of the oral administration of penicillin makes it one of the more desirable methods of administration of this antibiotic. Because the serum concentration of penicillin is irregular and generally low after this method of administration, it would seem inadvisable to use it in severe infections, in infections in which the causative micro-organisms are relatively resistant to penicillin or in infections in which the penicillin does not have easy access to the bacteria. The wisest procedure is to evaluate the usefulness of oral penicillin by extensive clinical trial in the various diseases in which it might, theoretically, be effective before recommending its use. Preferably, such studies should be controlled by the treatment of similar patients with comparable doses of penicillin administered parenterally.

We have used the oral method to treat 298 patients, most of whom were suffering from infections which were either mild or were caused by bacteria which were relatively susceptible to penicillin. Numerous patients with the same diseases have been treated by us with parenteral penicillin. Usually about one-fifth as much penicillin

was used by injection as was administered orally. In some instances alternate patients were given oral and parenteral penicillin. In others the route of administration depended upon the preparation available at the time. In no case was the selection of the route based upon the severity of the disease.

In the case of patients with pneumococcic pneumonia, streptococcic sore throat with rash (scarlet fever), streptococcic sore throat without rash, corynebacterium, otitis media, acute sinusitis and certain infections of the skin and subcutaneous tissues, there was no difference between the response obtained when penicillin was administered parenterally and when it was given orally in doses approximately five times as great. It will be noted that these infections were all caused by organisms which are usually inhibited by concentrations of penicillin sufficiently low to be obtainable in the serum when penicillin is given orally in doses of 75,000 to 125,000 units every three hours. On the other hand, oral therapy was not successful in two cases of bacterial endocarditis caused by *Str. viridans*. This result might be expected in view of the fact that these organisms are sometimes relatively resistant to penicillin and the lesions are not easily accessible to penicillin.⁵⁴

SUMMARY

1. Penicillin was administered by the oral route to 350 patients, and the results were compared with those obtained in over 600 patients treated by intermittent intramuscular injections. The oral doses were approximately five times as great as the parenteral doses.

2. The results were comparable to those obtained with parenteral therapy in the case of pneumonia, streptococcic sore throat, scarlet fever, corynebacterium and otitis media. They were less satisfactory in Vincent's stomatitis and poor in the case of bacterial endocarditis.

3. Hypersensitivity reactions were less frequent than with penicillin administered by the other commonly used routes.

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Hypertension and Urologic Disease^{*}

HOMER W. SMITH, SC.D.

New York, New York

NUMEROUS investigators in this country and abroad continue to study animals rendered hypertensive by interference with the renal blood flow, i.e., by one variation or another of the Goldblatt experiment. This experiment is among the classics of modern physiology and has evoked perhaps greater interest and a larger series of publications than any other single experiment of the last two decades. This is wholly appropriate and is to be expected in view of the great importance of hypertensive disease which affects one quarter or better of the adult population. The literature on experimental hypertension runs to well over a thousand papers. It has recently been summarized by several workers in that field^{22,46,49} and it is unnecessary to comment on it except in one or two details. Renin, presumed to be the precursor of the pressor substance in the initial stages of experimental hypertension, is demonstrable in the systemic blood for a short time following clamping of the renal arteries in dogs and also in man in circumstances where the renal blood flow is abruptly and markedly reduced; but in dogs with chronic hypertension, as well as in patients with essential hypertension, the most reliable results have been uniformly negative up to this time. If the renin mechanism is solely responsible for the rise in blood pressure in the early stages of the Goldblatt experiment, or in early renal hypertension in man, some other mechanism, apparently quite independent of the renin mechanism, is responsible in the chronic stages in both types. There is, there-

fore, no warrant to conclude that renin is the pressor factor in well established hypertensive disease, and we remain without any experimental interpretation of the chronic process in man. Nor is it yet demonstrated that the renin mechanism is responsible for early essential hypertension in man.

It was once thought that a unilateral Goldblatt kidney could activate a mechanism in the contralateral, unclamped kidney to produce hypertensive disease but it is now contended that this result is peculiar to the rat. It is very rare for a unilateral Goldblatt kidney to produce a substantial and sustained rise in pressure in the dog; the rise of pressure is at best only moderate and transient. There is therefore no warrant from experiments on dogs for assuming that unilateral renal disease in man can initiate chronic or self-propagating hypertension.

There is a considerable amount of literature on the renal blood flow in essential hypertension and in other pathologic processes in man, and nothing in these data points convincingly to the primacy of renal ischemia. The available data can be equally well interpreted in terms of a disease which produces afferent arteriolar sclerosis as well as functional constriction of the efferent glomerular arterioles (possibly by a humoral mechanism) and to which the kidneys become an easy victim possibly for no other reason than because they receive so large a fraction (approximately one-fifth) of the total cardiac output.

If we assume that hypertensive disease is the result of a multitude of microscopic

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Goldblatt clamps placed upon the renal arterioles in consequence of arteriolar sclerosis, then we must recognize that the arteriolar disease, which itself remains unexplained, is the primary event and there is no reason to limit this to the kidneys. As I have said before,¹¹³ it does not advance our problem and it is illogical to suppose that at one moment humoral agents are operating to reduce renal blood flow and then at the next moment suppose that the reduction in renal blood flow is the reason for the appearance of these agents in the blood.

Alternatively, there are those who argue that renal ischemia or some other disturbance in the renal circulation is brought about by neurogenic constriction of the renal arterioles mediated through the sympathetic nervous system. They imply, as yet without warrant, that the stresses of modern life initiate the hypertensive process along the lines of the Goldblatt experiment by functional vasoconstriction. It has been well demonstrated that severe alarm, pain close to the threshold of toleration and, more recently, neurotic conflict when abruptly precipitated^{89,110,111,123} can cause renal vasoconstriction in man, although it is not known how much of this vasoconstriction is attributable to neurogenic action and how much to the secretion of adrenalin. However, the surgeons report no success in reduction of blood pressure in hypertensive subjects by renal denervation; in order to achieve any significant reduction in pressure they must destroy almost all the sympathetic nervous system, the primary mechanism by which vasoconstrictor impulses are delivered to the arterioles throughout the body, and even here they are successful no more than about one-third of the time. In the absence of better evidence in favor of the functional vasoconstriction hypothesis and in the face of the stubborn chronicity of established hypertensive disease despite extensive destruction of the sympathetic nervous system, this hypothesis is at best a long guess.

The cause of essential hypertension is as yet unknown. I have previously drawn an analogy with diabetes mellitus.¹¹³ Had

someone placed a clamp on the pancreatic artery before the days of Minkowski and obtained diabetes, he might well have been led to the theory that all diabetes is due to pancreatic ischemia or some other disturbance in the pancreatic circulation. This is, of course, not true; it is probably a very rare case in which the pancreatic circulation plays any part; in some instances diabetes possibly can be attributed to a congenital deficiency of islet tissue, in some cases to pituitary dysfunction and in some cases possibly to a disturbance in the adrenal cortex. In the light of our present knowledge it is reasonable to believe that essential hypertension may also have several causes, or in other respects be as complex as diabetes.

The use of thoracicolumbar sympathectomy as a therapeutic measure is one of great interest to both internists and surgeons. I hesitate to cite statistics on so-called successes in sympathectomy because the statistics published by different investigators vary so widely. I have no hesitancy, however, in pointing out that sympathectomy deprives the body of an important mechanism for maintaining blood pressure and it is not as surprising that the pressure falls in some instances as that it should fail to fall in so many others. This failure points to widespread functional changes in the arteriolar bed throughout the body. No evidence has yet been presented that sympathectomy changes the temporal progress of the disease; perhaps some patients will live longer if the danger of cerebral accidents is reduced by lowering the pressure, but the danger of cerebral thrombosis and coronary thrombosis may possibly be increased. One of my colleagues has replied to the question, "When would you recommend sympathectomy in hypertension?" with the answer, "In desperation and experimentation." In the last sense it is unquestionably valuable, but we must await data on the life history of the experimental subjects before considering the experiment complete.

Lastly, I must remark on the unreliability

of the blood pressure itself. Every student of this problem recognizes the lability of pathologically increased blood pressure. A single reading is virtually worthless since blood pressure can be raised or lowered by a variety of unrelated factors. It is the practice among those who are interested in hypertensive disease to hospitalize the patient for two to four weeks and to make repeated blood pressure observations throughout the day before drawing a base line. A large proportion of hypertensive subjects will show a marked reduction in blood pressure, frequently to normal values, under conditions of hospitalization and bed rest. Only after obtaining a long drawn, careful base line may one attribute a reduction of blood pressure to any therapeutic measure. In recent studies in which hospitalized patients were maintained on a fairly standard regimen we have observed that as long as the research nurse took the pressure of certain patients it remained low, but let a physician, even one known to the patient, be in attendance and the pressure might soar to astonishing heights. Conversely, in some instances the nurse proved to be the pressogenic agent.

It is well known that in many patients the blood pressure can be materially lowered by psychotherapy,^{2,3} by reporting regularly to the clinic, by reduction in weight or other changes in living habits³⁶ and by disciplined relaxation,⁵⁹ although it may remain refractory to many quasi-specific therapeutic agents.⁶² Nor can any significance be attached to relief of symptoms. There is a paper by David Ayman² published seventeen years ago which is required reading for anyone interested in the therapy of hypertensive disease. Ayman reviewed thirty-five articles dealing with the treatment of hypertension and he pointed out that in practically every article complete or partial symptomatic relief was reported. Seldom was failure mentioned. The majority of papers reported a moderate reduction of blood pressure and a few reported a marked reduction. But it was consistently demonstrated that the degree of symptomatic

relief was greater than the reduction of pressure and symptomatic relief was frequently obtained without reduction of pressure. Included in the alleged therapeutic measures were irradiation of the suprarenal region, application of mistletoe, low salt diet, liver extract, radium to the skull, diathermy, corpus luteum, watermelon extract, subtonin, calcium salts plus low protein diet, benzylbenzoate, desincin, thyroid plus potassium permanganate, animasa, rhodan plus calcium plus diuretin, potassium and sodium sulfocyanate, nitroscleran, luminal, theominal, radium water and Nauhcim baths.

Ayman himself studied the effects of applying to forty hypertensive patients under ambulatory conditions the systematic therapeutic measure of making a complete history and physical examination and prescribing seriously and enthusiastically ten drops of dilute hydrochloric acid to be taken in one-half glass of water before meals, three times a day. Thirty-three out of the forty patients showed definite improvement ranging from partial to complete relief of symptoms, giving 82 per cent success. Although possibly neurotic, these symptoms are not imaginary: headache, insomnia, nervousness, fatigue, weakness, loss of appetite and dizziness were most commonly relieved, to which was added a general sense of well being. The majority of patients improved after taking the treatment for one week, but a few were not relieved until the therapy had been continued for three weeks. Only three untoward results were encountered: the medicine made one patient so tired that she had to lie down after taking it; in a second patient it was accompanied by generalized pruritus without any objective change in the skin and the third patient, after three days of therapy, was seized with such headache, nausea and vomiting, chilly feelings, weakness, pain and exhaustion that she had to remain in bed for one week. I repeat that Ayman's paper on the treatment of essential hypertension by dilute hydrochloric acid is required reading for all students of this

problem. As Ayman remarks, "Hundreds of articles have appeared on the successful treatment of hypertension by many different methods and drugs, none of which have any specificity. They all have one thing in common: the enthusiastic treatment of a worried patient."

Van Dyke,¹¹⁶ in discussing the Weapons of Panacea, quotes Trousseau's injunction, "Always use the new drugs while they still have power to heal," and notes that during the period of medical enthusiasm results can be highly successful; as doubts assail the therapist only an occasional patient is benefited; finally, the physician is frankly skeptical and the previously valuable drug becomes virtually worthless. This leads him to remark that even the laity are amused when the cartoonist depicts a druggist holding a vial before a prospective customer and saying, "It has been a wonder drug for over a week now."

In several places in the world primitive medicine men developed the art of trephining the skull with crude instruments. One may hazard the guess that this anatomic approach was initiated by the patient's complaint of headache and, to extend the guess, we may suppose that in some instances, the headache was related to hypertension. Judged by the success of the modern medicine man in relieving headache, insomnia, nervousness and other symptoms by non-specific measures, I think we can confidently believe that craniotomy was once equally successful in maintaining the prestige of the profession. In view of the therapeutic usefulness of dilute hydrochloric acid and other non-specific agents, caution is needed in accepting the specificity of such powerful medicines as sympathectomy and nephrectomy. It is rather too bad that we do not have a few living craniotomies for controls.

The fundamental trouble is that we have no method of evaluating the status of hypertensive disease, except in its malignant stage, other than by blood pressure; and blood pressure, even when repeatedly recorded over a protracted period, is a clinical

quicksand. For several years workers in my laboratory have devoted themselves to the task of obtaining better and more reliable criteria of cardiovascular disease and as time goes on I have increasing confidence that they have chosen a wise, if distant, goal.

We need not only a more reliable quantitative assessment but earlier recognition in the benign stage. It has been claimed that essential hypertension is an hereditary disorder or at least that a predisposition to hypertension is hereditary. But mammalian genetics, and particularly human genetics, is proving to be more complex than merely the presence or absence of a dominant gene; the same inherited feature may be variously dominant, recessive or sex-linked in different pedigrees; dominance and recessiveness are themselves not absolute and distinct but in different pedigrees the same gene may manifest itself by a sliding scale of values so that, quite apart from a tendency to skip a generation, so-called lack of penetrance, the same genetic character may have very different somatic effects in two different families.⁴⁴ At one extreme, hypertension or its predisposition may be hereditary in some such complex manner; at the other extreme, it may reflect the genetic make-up of the individual without being hereditary—a man may by chance draw a genetic-somatic pattern of such a nature that he is no longer able to fit his environment. What is one man's healthy environment may be another man's poison.¹¹² Moschkowitz⁷⁷ has argued that hypertension, along with Graves' disease, peptic ulcer, cardiospasm, manic-depressive psychosis and paranoia are hyperkinetic diseases arising in civilization. Perhaps we are finding that civilization is pathogenic for the normal man.

The psychiatrist, as I have intimated, believes that he, too, has an interest in this problem, and well he may. The art of getting devils out of the head is an ancient and honorable one, as witness the holes in many prehistoric skulls. There are times when I am apprehensive that we are headed for a civil war in medicine between internal medicine, well established on objective

observation and the experimental method, on the one hand, and its younger and more fancy-free sister sciences, psychiatry and psychosomatic medicine, on the other. Should my apprehension become a reality, it may come about that from the smoke and noise of the battle, the charges and counter-charges inevitably to be hurled, when the laity may well come to question whether either side knows what it is talking about, the urologist will emerge the hero when he proclaims "Well, I once had a case . . . and I took one kidney out . . . and I cured high blood pressure." It is our task to calculate the probabilities of that happy event.

First, let us consider the incidence of hypertension in the general population. (Table 1.) The criteria of hypertension and the conditions of blood pressure observation have varied so much that data from various clinics are not strictly comparable; moreover, many statistics, for example those collected with life insurance applications, may represent single observations. Unfortunately, one cannot improve the accuracy of inadequate statistics by multiplying their number and these data must be accepted only as approximations.

The figures of Master et al.,⁷¹ representing 14,849 persons, are based in part upon people gainfully employed, in part upon residents in homes for the aged and in part upon hospital patients; except for the absence of data for ages less than forty, they possibly represent the best cross section available for the population in the middle and later age groups. (The authors review the literature on this subject.) No differentiation is made between arteriosclerosis and essential hypertension and failure to make this distinction is characteristic of most of the available data. All investigators have recognized the increasing incidence of hypertension with advancing age, but Master and his colleagues emphasize the surprisingly high incidence in persons over forty years of age. The figures are, of course, larger if the criterion of 140/90 instead of 150/90 is used. They estimate from popula-

tion statistics that one-half of the male population of the United States and 60 per cent of the female population of forty years of age or over are hypertensive. The data of Robinson and Brucer¹⁰¹ cannot be presented in a comparable manner because of the use

TABLE 1
INCIDENCE OF HYPERTENSION IN THE GENERAL POPULATION

	Age	Per Cent Hypertensive		
		Male	Female	Both Sexes
Master, Marks and Daek ⁷¹ 14,849 miscellaneous persons (150/90 mm. or over)	40-49 50-59 60-69 70-79 40 and over	25.9 40.6 56.3 65.5 40.9	32.0 53.4 67.7 73.3 50.7	
Robinson and Brucer ¹⁰¹ 10,883 insurance policy holders, adults only (140/90 mm. or more?)	40.0
Friedman, Moschkowitz and Marrus ⁴² 1,006 living controls. (Diastolic 100 mm. Hg or over, or diastolic of 90 mm. and systolic 150 mm. or over.)	30-39 40-49 50-59 60-69 70-79 30-79	10.2 26.0 34.0 47.5 51.0 24.7
Braasch, Walters and Hammer ²⁰ 975 clinic registrations (Systolic 145 mm. or over)	Less than 20 20-29 30-39 40-49 50-59 60-69 70 or over 30 and over	0 2.1 8.4 16.4 28.7 47.4 53.1 25.0
Shure ¹⁰⁹ 947 random selections from 11,898 autopsy reports 150/95 mm. or over or cardiac hypertrophy)	Under 30 31-40 41-50 51-60 over 60 All ages	21.4 25.5 39.8 33.5 43.7	10.0 30.6 40.2 43.1 42.1	15.6 28.1 40.0 36.6 43.1 34.9
Oppenheimer, Klemperer and Moschkowitz ⁸⁴ 333 cases. Every 15th patient in series of 5,000 coming to autopsy (155/95 mm. or over)	24.0
Baggenstoss and Barker ⁴ 100 control necropsies (150/90 or over and cardiac hypertrophy)	29.0
Emerson and Irving ³⁸ 1,020 employed males, 21 to 78 years (criteria not given)	11.8?

of independent systolic and diastolic criteria, but these authors state that slightly more than 40 per cent of the adult population is actually or incipiently hypertensive.

Friedman, Moschkowitz and Marrus⁴⁷ give data from 1,006 consecutive patients admitted to the combined surgical services (other than genitourinary service) of the

Mt. Sinai Hospital, excluding patients with severe anemia, high fever or coronary occlusion. Males and females are about equally represented. The data of Braasch, Walters and Hammer²⁰ are based on 975 consecutive patients taken at random from registrations at the Mayo Clinic. In both series the rising incidence with age is evident. The average figure of 25 per cent is lower than the 40 per cent indicated by the previous two series, largely because of the inclusion of the younger age group, thirty to thirty-nine.

Perhaps it is only a rhetorical question to ask whether or not patients requiring surgical or medical attention are representative of the general population. This question is certainly pertinent to the data of Shure,¹⁰⁹ Oppenheimer, Klemperer and Moschkowitz⁸⁴ and Baggenstoss and Barker,⁴ which are based upon autopsy records. These represent patients who came to the hospital mortally sick and as such are not truly representative of the general population. Illness, and particularly fever, may actually have reduced the blood pressure in many patients. Aside from this criticism the figures warrant the conservative statement that the incidence of hypertension, quite low before the age of twenty, increases rapidly thereafter until at the age of forty approximately 25 per cent of the general population are hypertensive, this figure increasing to 60 per cent or above in elderly persons.*

I turn now to the incidence of hypertension in patients with urologic disease, as shown in Table II. For ease of discussion the data are arranged by urologic classification rather than by priority of publication.

Rath and Russek,⁹² comparing merchant seamen with and without urologic disease (chiefly nephrolithiasis, ureteral lithiasis, hydronephrosis and prostatic hypertrophy,

* Emerson and Irving³⁶ state that among the first 1,020 men applying for "physical fitness service" there were 120 with hypertension, the criteria for which are not stated. No breakdown is given by age and it may be that the low incidence of hypertension is attributable to the preponderant number of young persons; otherwise the data are disparate with those given by other observers.

TABLE II
INCIDENCE OF HYPERTENSION IN PATIENTS
WITH UROLOGIC DISEASE

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Rath and Russek ⁹²	(357)	(654)
Systolic above 145 mm. with diastolic 94 mm. or below		
10 to 49 years.....	4.36	3.52
50 to 89 years.....	25.78	32.28
Diastolic above 95 mm.		
10 to 49 years.....	5.24	5.41
50 to 89 years.....	17.96	21.75
Sarnoff ¹⁰³		
70 with one or both pelvis intrarenal.....	38	
106 with both pelvis extrarenal..	37	
Stofer and Kline ¹¹⁴		
38 with one or both pelvis intrarenal.....	37.0	
38 with pelvis extrarenal.....	39.5	
Shrader, Young and Page ¹⁰⁸		
100 pyelographic abnormalities..	22.0	
Braasch and Goyanna ¹⁷		
133 nephroptosis.....	11.8	
Ritter ¹⁰⁰		
28 urologic developmental anomalies.....	14.2	
24 developmental anomalies, hydronephrosis or stone with or without infection, observed 5 to 10 years; blood pressure normal at first observation.....	0.0	
Campbell ²⁶		
173 prostatism.....	11.0	
Friedman, Moschkowitz and Marrus ⁴²		
25 hydronephrosis.....	36.0	
Braasch, Walters and Hammer ²⁰		
372 hydronephrosis all ages.....	13.7	
hydronephrosis under 50 years of age.....	7.7	
577 hydronephrosis with stone...	20.9	
Baggenstoss and Barker ⁴		
28 hydronephrotic atrophy.....	25.0	
Oppenheimer, Klemperer and Moschkowitz ⁸⁴		
66 unilateral hydronephrosis or pyelonephritis.....	32.0	
Abeshouse ¹		
4 hydronephrosis, uncomplicated..	0.0	
16 hydronephrosis, complicated..	18.7	
Braasch and Wood ²¹		
70 perinephritis.....	4.3	
Ellis and Evans ³⁵		
Renal dwarfism.....	Rare	
Friedman, Moschkowitz and Marrus ⁴²		
32 tuberculosis.....	15.6	

TABLE II (Continued)

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Braasch, Walters and Hammer ²⁰		
158 tuberculosis.....	7.6	
Crabtree and Chaset ³⁰		
23 tuberculosis.....	4.4	
Abeshouse ¹		
15 tuberculosis.....	20.0	
Braasch, Walters and Hammer ²⁰		
111 miscellaneous.....	18.0	
Friedman, Moschkowitz and Marrus ⁴²		
7 miscellaneous.....	0.0	
Abeshouse ¹		
3 traumatic.....	0.0	
13 miscellaneous.....	7.6	
Oppenheimer, Klemperer and Moschkowitz ⁸⁴		
18 unilateral narrowing of renal artery.....	83.0	
97 unilateral hypoplasia.....	23.0	
Baggenstoss and Barker ⁴		
13 unilateral hypoplasia.....	15.3	
Braasch, Walters and Hammer ²⁰		
164 nephrolithiasis with infection.....	22.5	
52 nephrolithiasis without infection.....	5.7	
Shure ¹⁰⁹		
62 nephrolithiasis.....	53.2	
Friedman, Moschkowitz and Marrus ⁴²		
60 neoplasms.....	28.3	
Braasch, Walters and Hammer ²⁰		
137 adenocarcinomas.....	27.7	
Crabtree and Chaset ³⁰		
41 hypernephroma.....	14.6	
Abeshouse ¹		
24 neoplasms.....	12.5	
Morlock and Horton ⁷⁶		
240 hypernephromas, males.....	39.2	
88 hypernephromas, females.....	53.5	
76 males with other renal tumors.....	40.8	
48 females with other renal tumors.....	54.2	
Braasch and Jacobson ¹⁸		
180 bilateral pyelonephritis.....	26.0	20.0
Shure ¹⁰⁹		
224 bilateral pyelonephritis.....	47.7	
66 unilateral pyelonephritis.....	33.3	
Entire series of 290 patients:		
Under 30 years of age (controls).....	28.0	15.6
31-40 years of age (controls).....	33.3	28.1
41-50 years of age (controls).....	41.0	40.0
51-60 years of age (controls).....	49.0	36.6
Over 60 years of age (controls).....	63.0	43.1
All ages.....	44.4	34.9

no specific breakdown being given), report the same incidence of hypertension in 357 men with uropathologic conditions and 654 controls. Although the authors give a breakdown by decades, it is sufficient to note that the incidence of hypertension is the

TABLE II (Continued)

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Pearman, Thompson and Allen ⁸⁷		
500 pyelonephritis (unilateral and bilateral).....	9.0	
(500 goiter without hyperthyroidism.....		10.0
(500 gallbladder disease.....		7.0
Crabtree and Chaset ³⁰		
76 unilateral pyelonephritis.....	9.2	
Abeshouse ¹		
9 acute unilateral pyelonephritis..	11.1	
9 chronic unilateral pyelonephritis	11.1	
21 pyonephrosis.....	14.2	
Friedman, Moschkowitz and Marrus ⁴²		
69 unilateral pyelonephritis.....	15.8	
Braasch and Jacobson ¹⁸		
119 less than 50 years of age with bilateral pyelonephritis.....	16.8	
606 controls less than 50 years of age.....		9.1
61 over 50 years of age with pyelonephritis.....	44.2	
369 controls over 50 years of age..		37.9
Braasch, Walters and Hammer ²⁰		
43 pyelonephritic atrophy.....	46.5	
70 pyelonephritis other than atrophic.....	18.6	
Baggenstoss and Barker ⁴		
48 pyelonephritic atrophy.....	39.6	
8 pyonephrotic atrophy.....	37.5	
100 controls.....		29.0

same in both groups before and after the age of fifty. They state that they are unable to demonstrate an association between urologic disease and hypertension.

Ravich⁹⁵ believed that the intrarenal type of pelvis is regularly associated with hypertension, but this has been questioned by Sarnoff¹⁰³ whose data show a lower incidence (38 per cent) in seventy persons with one or

both pelves intrarenal than in 106 persons (47 per cent) with both pelves extrarenal. Sarnoff concludes that there is no correlation between the two conditions. Similarly, Stofer and Kline¹¹⁴ find the same incidence in a series of thirty-eight patients with unilateral or bilateral intrarenal pelves as in thirty-eight controls with extrarenal pelves, and again conclude that no correlation can be demonstrated.

Shrader, Young and Page¹⁰⁸ report an incidence of hypertension of only 22 per cent in one hundred subjects exhibiting obvious pyelographic abnormalities such as hydronephrosis, ptosis, polycystic disease, lithiasis and congenital anomalies, a figure which they consider to be not above the normal probability. Braasch and Goyanna¹⁷ conclude that nephroptosis is seldom if ever an etiologic factor, while Ritter¹⁰⁰ concludes that hydronephrosis, whether or not complicated by stone or infection, does not lead to hypertension. In a series of twenty-four patients with developmental anomalies (hydronephrosis or lithiasis with or without infection) who were observed for five to ten years, the blood pressure being normal at the first observation, none developed hypertension in this interval although many had recurrent urinary infection or lithiasis. Campbell²⁶ finds an incidence of 11 per cent of hypertension in 173 patients with prostatic hypertrophy, a figure which is hard to explain when the incidence of hypertension in unselected groups of men old enough to have prostatism should be 50 per cent or better. From the data of Friedman, Moschkowitz and Marrus,⁴² Braasch, Walters and Hammer,²⁰ Baggenstoss and Barker,⁴ Oppenheimer, Klemperer and Moschkowitz,⁸⁴ and Abeshouse,¹ hydronephrosis does not appear to be a predisposing cause. Braasch and Wood²¹ find an incidence of only 4.3 per cent in seventy cases of clinical perinephritis, most of the patients being under fifty years of age, a figure which they state to be less than one-half of that in a random sample of controls in the same age group. Ellis and Evans³⁵ note that the incidence of hypertension in renal dwarfism is rare. Hyper-

tension had no undue frequency in renal tuberculosis (Friedman, Moschkowitz and Marrus,⁴² Braasch, Walters and Hammer,²⁰ Crabtree and Chaset,³⁰ or Abeshouse¹) and in miscellaneous cases reported by Braasch, Walters and Hammer,²⁰ Friedman, Moschkowitz and Marrus⁴² and Abeshouse.¹ Blackman¹¹ emphasized the high incidence of arteriosclerotic plaques in the renal arteries of a series of fifty cases of hypertension coming to necropsy, and Oppenheimer, Klemperer and Moschkowitz⁸⁴ report that of eighteen subjects shown at necropsy to have unilateral narrowing of the renal artery, 83 per cent had hypertension; but the latter authors were led to the conception that hypertension of unknown origin had resulted in general arteriosclerosis and to the accidental deposition of a plaque in a renal artery. Thirteen of the fifteen positive cases also showed arteriosclerosis of the aorta. The pathologic condition of the artery could not be held to be causal to the hypertension. These same investigators and Baggenstoss and Barker,⁴ find no correlation between hypertension and unilateral hypoplasia. Braasch, Walters and Hammer²⁰ find no correlation with nephrolithiasis without infection; the figure is greater when infection is present, but still is not statistically significant. Shure¹⁰⁹ reports 53 per cent of hypertension among sixty-two patients with nephrolithiasis, without commenting on the absence or presence of infection, but 83 per cent of Shure's hypertensive patients were forty years of age and 40 per cent of them were over sixty. The figure 53 per cent is therefore in line with older age groups without specific renal pathologic disease. Renal neoplasms appear to cause no undue incidence of hypertension according to Friedman, Moschkowitz and Marrus,⁴² Braasch, Walters and Hammer,²⁰ Crabtree and Chaset³⁰ and Abeshouse.¹ Higher figures are reported by Morlock and Horton,⁷⁶ but these writers note that by comparison with other renal tumors hypernephroma exhibits no specificity.

Up to this point the evidence is interpreted as negative by nearly all the writers

mentioned: that is, the incidence of hypertension in the urologic conditions enumerated is no greater than, and it frequently is less than, the incidence to be expected by chance as judged by the frequency of the disease in the general population without urologic disease. It is frequently stated that bilateral pyelonephritis is conducive to hypertension, yet the statistics do not bear this out. Braasch and Jacobson¹⁸ report an incidence of 26 per cent in 180 such cases, a figure which is to be compared with 20 per cent in their control series. At one extreme Shure¹⁰⁹ reports 47.7 per cent when the disease is bilateral, but of the hypertensive patients, 64 per cent were over fifty-one years of age and 82 per cent were over forty-one. Compared by decades with Shure's 947 controls or with other controls, there is little indication of specificity. At the other extreme, Pearman, Thompson and Allen⁸⁷ report only 9 per cent in a series of 500 cases with no breakdown as between unilateral and bilateral infection, a figure not only surprisingly low but no higher, as the authors note, than in a comparable series of goiter and gallbladder disease. A similarly low incidence in unilateral pyelonephritis is reported by Crabtree and Chaset,³⁰ Abehouse¹ and Friedman, Moschowitz and Marrus.⁴² Crabtree and Chaset express the view that the pathologic and anatomic elements seem less important in this problem than an as yet unknown physiologic element. Braasch and Jacobson¹⁸ find a greater incidence of hypertension in pyelonephritis than in their own control series, both before and after the age of fifty. Although they are inclined to the belief that chronic bilateral pyelonephritis exercises a definite influence on the incidence of hypertension, especially among patients less than fifty years of age, the indication falls short of proof relative to the other statistics. Braasch, Walters and Hammer²⁰ and Baggenstoss and Barker⁴ record a high incidence of hypertension in unilateral pyelonephritic atrophy and Baggenstoss and Barker⁴ in unilateral pyonephrotic atrophy. Both groups of workers lean to the

belief that a causal relationship is indicated by these statistics.

With these possible exceptions, namely, pyelonephritic and pyonephrotic atrophy, the above data do not indicate that urologic disease increases the incidence of hypertensive disease, or that in any large number of instances it is causally related to its genesis. Hines and Lander⁵³ report that among 264 patients with urologic disease, who were observed over a period of ten years or more (average 15.3 years), the incidence of hypertension either prior to or subsequent to the first observation was practically identical with a control series of 790 patients without urologic disease. Hines and his co-workers have emphasized the hereditary aspects of hypertensive disease and believe that hereditary factors are more important than any type of renal involvement.

To complete the literature on this subject, I turn briefly to papers dealing with the incidence of urologic abnormalities in otherwise unselected hypertensive patients. (Table III.) The earlier papers of Longcope⁷⁰ and of Weiss and Parker,¹¹⁰ suggesting a significant correlation between pyelonephritis and hypertension, coupled with the rapidly expanding literature on the Goldblatt experiment and Butler's²⁵ report of reduction of blood pressure by unilateral nephrectomy in an eight year old girl, led investigators to suspect that urologic disease, sometimes of an apparently minor nature, might be the origin of this obscure pathologic process.

In 1941, Schroeder and Steele¹⁰⁵ reported that of 250 living patients with hypertension, 113 or 45 per cent, showed urologic disease of one kind or another. On reviewing their evidence in 1943, however, my colleagues and I noted that fifty-three patients of these 113 positives had bilateral disease, eight had glomerulonephritis, seventeen had bilaterally abnormal pyelograms and there were twenty-eight in whom bilateral renal disease was suspected though not proven, leaving only 60 of 250 or 24 per cent with possible, but unproved, unilateral

disease.¹¹³ Moreover, judgment of urologic fault in Schroeder and Steele's series was based largely upon abnormal radiograms obtained by intravenous or retrograde

TABLE III
INCIDENCE OF UROLOGIC DISEASE IN HYPERTENSION
Per Cent with
Urologic Disease

Schroeder and Steele ¹⁰⁵	
250 hypertensives, (pyelographic).	45 0
After selection by Smith, Goldring and Chasis	24 0
Wosika, Jung and Maher ¹²⁴	
568 necropsies, no selection	40 0
Hayes and Ashley ⁵¹	
55 hypertensives (urographic)	51 0
Flocks ⁴⁰	
132 hypertensives (pyelographic)	15 0
Palmer, Chute, Crone and Castleman ⁸⁵	
212 hypertensives (pyelographic)	22 0
Sarnoff ¹⁰³	
50 hypertensives (one or both intrarenal pelves)	40 0
100 normotensives (one or both intrarenal pelves)	30 0
Hyman and Schlossmann ⁵⁸	
55 necropsies	no correlation with intrarenal pelves, calculi or hydro-nephrosis
200 pyelograms	
Shiadr, Young and Page ¹⁰⁸	
114 hypertensives (abnormal renal pelves)	19 0
Ratliff and Conger ⁹³	
188 hypertensives with urinary symptoms (pyelographic) . . .	25 5
340 hypertensives without urinary symptoms (pyelographic) . .	9 4
Ratliff, Nesbit, Plumb and Bohne ⁹⁴	
2,055 hypertensives (pyelographic)	8 9
Bechgaard ⁸	
1,038 hypertensives (pyelonephritis and urolithiasis)	7 7
Pearman, Thompson and Allen ⁸⁷	
12,000 hypertensives (500 only had urologic examination, the other 11,500 giving no history of renal disease)	3 2
Braasch ¹⁶	
4,000 hypertensives (routine clinical examination)	2 5
Lisa, Eckstein and Solomon ⁶⁹	
56 hypertensives	caliber of renal arteries same as in 44 controls
Chasis and Redish ²⁷	
21 hypertensives	no unilateral anomalies or unilateral decrease in function

pyelography, and Chasis and Redish²⁸ have shown that the pyelogram is a hazardous basis for the diagnosis of abnormality since an innocuous angulation of the ureter or

dilatation of the pelvis can give the impression of abnormality, although there is actually no obstruction of the lumen or functional evidence of renal impairment. The significance of many of the residual sixty cases presented by Schroeder and Steele's series is therefore open to some doubt. Wosika, Jung and Maher¹²⁴ reported urologic abnormalities in 227 out of 568 necropsies of hypertensive subjects, or an incidence of 40 per cent, a figure to be compared with 27.4 per cent in 611 control necropsies. These authors included all types of unilateral and bilateral disease and their criterion of hypertension rested solely upon the systolic pressure; for these reasons the significance of their calculation is open to question. Hayes and Ashley⁵¹ reported twenty-eight out of fifty-five abnormalities (including meatal stenosis, urethral stricture and urethral angulation) or 51 per cent, but the alleged abnormalities were not such as to be associated invariably with disturbed renal function.

More moderate estimates are given by Flocks⁴⁰ who reported 20 of 132 pyelographic abnormalities, or 15 per cent,* and Palmer, Chute, Crone and Castleman⁸⁵ who report 47 of 212 pyelographic abnormalities, or 22 per cent (unilateral in 16 per cent). These figures are less than the 27 per cent incidence reported by Wosika, Jung and Maher in their 611 controls.

Sarnoff¹⁰³ reports the presence of one or both intrarenal pelves in 40 per cent in a series of fifty living hypertensives, but he finds an incidence of 30 per cent in one hundred controls and considers that the difference is not significant. Similarly, Hyman and Schlossman⁵⁸ report the incidence of intra- and extrarenal pelves in fifty-five autopsied patients who had hypertension. Shrader, Young and Page¹⁰⁸ report the presence of pyelographic abnormalities in 22 out of 114 living hypertensives or 19 per cent and note that it is practically

* Flocks reports reduced phenolsulfonephthalein excretion in 20 of 23 hypertensive patients but this is to be expected in view of the decrease in renal function characteristic of the disease.

difficult to obtain a control series of pyelograms, because such normotensives as are subjected to urologic study generally have urologic abnormalities. They point out, however, that out of one hundred pyelograms exhibiting obvious abnormalities, only 22 per cent of the patients were hypertensives.

Ratliff and Conger⁹³ found that 25.5 per cent of 188 hypertensive patients who showed urinary symptoms had pyelographic abnormalities, but the incidence of such abnormalities was only 9.4 per cent among 340 hypertensives without urinary symptoms.

Still more conservative are the data of Ratliff, Nesbit, Plumb and Bohne⁹⁴ who found an 8.9 per cent incidence of urologic disease in 2,055 hypertensives, of which number 1,350 were examined solely in an effort to determine a possible renal cause for hypertension; of Bechgaard,⁸ who found 7.7 per cent cases of pyelonephritis and urolithiasis in 1,038 living hypertensives and of Pearman, Thompson and Allen,⁸⁷ who found that among 12,000 patients who had hypertension 500 only gave a history of renal disease such as to lead to intravenous urologic examination; of the total series only 3 per cent had urologic disease. Admittedly, some urologic abnormalities may have been overlooked among those who did not receive urographic study, but such must have been minor affections.

Similar statistics have been reported by Braasch.¹⁶ Among 4,000 hypertensive patients he found clinical evidence of a non-nephritic renal lesion in approximately one hundred, or 2.5 per cent. Hyman and Schlossman⁵⁸ record their opinion that there is no correlation between intrarenal pelvis, calculi or hydronephrosis and hypertension, and Lisa, Eekstein and Solomon⁶⁹ found the caliber of the renal arteries in fifty-six consecutive hypertensive cases the same as in forty-four controls. In only two instances of the fifty-six did a renal artery show extreme stenosis.

Rath and Russek⁹² add together the statistics of Palmer and his co-workers, Ratliff and Conger, Braasch, Schroeder and

Steele and others and they note that of a total of 6,044 hypertensive patients, 10.7 per cent exhibit evidence of urologic disease. They contrast this figure to the 27.4 per cent incidence in normotensives reported by Wosika, Jung and Maher and conclude that the incidence of urologic disease among hypertensives is not greater, and possibly less, than among normotensive subjects.

Lastly, Chasis and Redish,²⁸ in clearance studies of twenty-one hypertensive subjects selected at random, demonstrated that renal functional impairment proceeds to an equal degree or at a parallel rate in both kidneys, a circumstance to be expected if renal injury is a result of the hypertensive process, but not if renal pathologic disease is primary. This evidence has always seemed to me to be the most convincing demonstration that in the majority of instances the kidneys are the victim and not the culprit in this disease.

To conclude on the basis of the above data that perhaps as many as 10 per cent of hypertensive patients have demonstrable urologic abnormalities of such a nature as to lead to functional impairment (and the figure 10 per cent seems generous in view of the data of Ratliff, Bechgaard, Pearman, Braasch and their co-workers), is no warrant for inferring that in these 10 per cent the urologic disease is responsible for the hypertension. The probability of coincidence is very great. At the present time the only way a causal relationship can be demonstrated in any particular case is by curing the hypertension by removing the offending organ. When my colleagues and I reviewed this question four years ago we found that of seventy-six instances of unilateral nephrectomy reported in the literature there were only seven that fulfilled our criteria for a lasting and significant reduction in blood pressure by the removal of the diseased kidney.¹¹³ About six months later Sensenbath¹⁰⁷ published a review which had been prepared without knowledge of our paper. He covered nearly the same literature and concluded that out of a total of seventy-five cases only five fulfilled his criteria for

TABLE IV
SUMMARY OF UNILATERAL NEPHRECTOMIES IN HYPERTENSIVE DISEASE

Author	Effects on Blood Pressure			
	No Significant Reduction	Reduced, But Not to Normal	Reduced to Normal Observation Less Than One Year	Reduced to Normal for One Year or More
Butler ²⁵	1
Boyd, Holmes and Lewis ¹⁴	1	
Barney, Dellinger and Suby ⁶	1
Bothe ¹³	1	1	..	
Kerr ⁸⁴	4	2	..	1
McIntyre ⁷⁴	1
Mulholland ⁸⁰	1			
Oppenheimer, Klemperer and Moschkowitz ⁸⁴	..	1		
Barker and Walters ⁵	..	2	3	
Bartels and Leadbetter ⁷	1
Crabtree and Chaset ³⁰	10	1
Everett ³⁷	1	3		
Horton ⁵⁵	1
Howard, Forbes and Lipscomb ⁵⁷	(1)*
Palmer, Chute, Cronc, Castleman ⁸⁵	8	1		
Patch, Rhea and Codnere ⁸⁶	1
Schroeder and Fish ¹⁰⁴	5	2		
Abeshouse ^{1†}	6	5		
Benjamin and Ratner ⁹	1			
Burkland ²⁴	1
Newbit and Ratliff ⁸²	4	1	6	
Onell and Munoz ⁸³	1	
Richardson and Smart ⁹⁷	..	1	1	
Braasch and Wood ²¹	2‡			
De Takats, Heyer and Keeton ³⁴	1	1§	1	
Farrell and Young ³⁸	1
Friedman, Moschkowitz and Marruss ⁴²	26	2
Friedman, Meyer, Selzer, Kreutzmann and Sampson ⁴³	2	3		
Gibson ⁴⁶	1	
Powers and Murray ⁹⁰	1
Ratliff and Conger ⁹³	3	3	3	
Riskind, and Greene ⁹⁹	..	14		
Wilson and Chamberlain ¹²²	1
Hotchkiss and Gilgrain ⁵⁶	1			
Jeck, Hotchkiss and Geary ⁶⁰	1			
McMartin and McCurdy ⁷⁵	..	3	..	1
Sweeney and Pace ¹¹⁶	1
Weiss and Chasis ¹¹⁸	1			
White, Durkee and Mirable ¹²¹	1
Besson ¹⁰	1
Dean and Abels ³³	1
Higbee ⁵²	..	1	..	1
Leiper ⁶⁷	1
Mosenthal ⁷⁸	1
Movin, Ohlsen and Pedersen ⁷⁹	1
Semens ¹⁰⁶	1
Sensenbach ¹⁰⁷	3	1
Kennedy, Barker and Walters ⁶³	1
Perry ³⁸	2
Wallace ¹¹⁷	2	1	..	2
Kittredge and Brown ⁶⁵	2	2		
Crosbie and Fischmann ³²	11			

(Table IV concluded on p. 736)

significant and lasting reduction of blood pressure. Both Sensenbaech and ourselves required that the blood pressure be lowered to or below 140/90; we required that it remain within normal limits for at least one year, while Sensenbaech required two years.

reduction in blood pressure, cases in which the pressure was reduced but not to normal, cases in which the pressure was reduced to normal but the observation period was for less than one year and cases in which the blood pressure was reduced to normal for

TABLE IV.—Continued

Author	Effects on Blood Pressure			
	No Significant Reduction	Reduced, But Not to Normal	Reduced to Normal, Observation Less Than One Year	Reduced to Normal for One Year or More
Kreutzmann ⁶⁶	2			
Ratliff, Nesbit and Plumb and Bohnc ⁹⁴	26	8	..	15
Wattenberg 	1		
Petch 	1			
Drew 	1
Langley and Platt 	10	1
	135	43	17	47

* Bilateral lumbar sympathectomy, probably chronic diffuse glomerulonephritis.

† Includes five questionably hypertensive individuals.

‡ One incomplete observation.

§ Inadequately reported.

|| Details on the patients reported by Ratliff et al.⁹⁴ are given by Nesbit (*Brooklyn Hosp. J.*, 5: 5, 1947). The writer has excluded by definition two cases (M. S. and R. K.) which these authors considered successful.

Since preparation of this manuscript, the writer has seen the papers of Langley and Platt (Langley, G. J. and Platt, R. *Quart. J. Med.*, 16: 143, 1947) who report a successful result in an eight year old child with congenital hypoplastic kidney, and he has received by personal communication from Dr. Edwin J. Drew of New York Hospital the report of a successful operation in the case of an eight year old girl with a pyelonephritic kidney.

Wattenberg (*Ann. Int. Med.*, 25: 734, 1946) reports what we consider a doubtful case, Petch (*Brit. Med. J.*, 4527: 547, 1947) reports one negative case, and Langley and Platt report ten negative cases. These data are included in Tables iv, v and vi.

Movin, Ohlsen and Pedersen⁷⁹ cite four cases in Danish literature not immediately available to the writer.

Since that time this literature has expanded and, although several articles contain excellent reviews, it is profitable to bring this topic up to date.*

In Table iv are listed the results of 242 operations recorded† under Sensenbaech's four categories: cases which have shown no

* Kreutzmann⁶⁶ records that he has reviewed every case published up to 1946, and found fifty-four patients in whom the pressure was reduced to below 150/90 for one year or longer. It must be noted, however, that he considers the two subjects reported by him as positive whereas we consider them as negative since the blood pressure remained at 156/94 and 170/100 respectively.

† Movin, Ohlsen and Pedersen⁷⁹ cite four additional cases in Danish literature not immediately available to the writer.

one year or longer. This last group constitutes what we may call "cures" of renal hypertension effected by unilateral nephrectomy. There are now on record reasonably well documented accounts of forty-seven such successful cases. Since in reviewing this literature I have made a selection according to certain specified criteria, I have been unable to include several to which only general reference is made. The operation appears to have been successful 19 per cent of the time.

In Table v these forty-seven successful operations are listed, and Table vi gives a summary of pathology. Braasch and his

TABLE V

RENAL PATHOLOGY IN CASES IN WHICH UNILATERAL NEPHRECTOMY HAS BEEN SUCCESSFUL IN REDUCING BLOOD PRESSURE

Author	Pathology	Age at Operation
Butler ²⁵	Calculus-pyelonephritis	8
Barney, Dellinger and Suby ⁶	Pyelonephritis	10
Kerr ⁸⁴	Congenital hypoplasia	16?
McIntyre ⁷⁴	Pyelonephritis	36
Bartels and Leadbetter ⁷	Hydronephrosis	37
Crabtree and Chaset ³⁰	Hypernephroma	?
Horton ⁵⁵	Hypernephroma	50
Patch, Rhea and Codnere ⁸⁶	Pyelonephritis	12
Burkland ²⁴	Ectopic kidney with arterial occlusion	5½
Farrell and Young ³⁸	Hematogenous cyst	18
Friedman, Moschkowitz and Marrus ⁴²	Tuberculosis	?
	Pyelonephritis	?
Powers and Murray ⁹⁰	Pyelonephritis	6
Wilson and Chamberlain ¹²²	Pyelonephritis	12
McMartin and McCurdy ⁷⁵	Pyelonephritis	39
Sweeney and Pace ¹¹⁵	Pyelonephritis	1
White, Durkee and Mirable ¹²¹	Hydronephrosis	39
Besson ¹⁰	Pyelonephritis	34
Dean and Abels ³³	Radiation sclerosis	28
Higbee ⁵²	Congenital hypoplasia	12
Leiper ⁶⁷	Tuberculosis and Atherosclerosis	18
Mosenthal ⁷⁸	Atrophic kidney with ureteral occlusion	37
Movin, Ohlsen and Pedersen ⁷⁹	Pyelonephritis	6
Semans ¹⁰⁶	Pyelonephritis	2½
Sensenbach ¹⁰⁷	Ureteral occlusion	41
Kennedy, Barker and Walters ⁶³	Pyelonephritis	7
Perry ⁸⁸	Infarct	32
	Infarct	20
Wallace ¹¹⁷	Pyelonephritis	43
	Pyelonephritis	37
Langley and Platt*.....	Congenital hypoplasia	8
Drew*.....	Pyelonephritis	8
Nesbit*.....	Pyelonephritis	21
	Pyelonephritis	49
	Pyelonephritis	52
	Pyelonephritis	42
	Hypernephroma	56
	Pyonephrosis	13
	Pyonephrosis	60
	Tuberculosis	27
	Pyonephrosis	51
	Pyelonephritis	41
	Hydronephrosis	30
	Hydronephrosis	24
	Hydronephrosis	20
	Pyonephrosis	50
	Pyelonephritis	49
	Total	47 cases

* See Footnote || at end of Table IV.

colleagues have expressed the opinion that among those rare cases suitable for operation the best results are to be expected in unilateral, atrophic pyelonephritis.

In Table VII these operations are listed by age. Although seventeen successes are

TABLE VI	
PATHOLOGY IN SUCCESSFUL UNILATERAL NEPHRECTOMY	
	No. of Cases
Pyelonephritis.....	22
Hydronephrosis.....	5
Pyonephrosis.....	4
Hypernephroma.....	3
Tuberculosis.....	3
Arterial occlusion.....	1
Hematogenous cyst.....	1
Ureteral occlusion.....	2
Infarct.....	2
Congenital hypoplasia.....	3
Radiation sclerosis.....	1
Total.....	47

reported in persons under twenty years of age, twenty-four were in their fourth or later decade. The rise in the percentage of successes from 9 per cent four years ago to 19 per cent as of this date may merely reflect the fact that as more nephrectomies have been performed, better selection of patients has been made. On the other hand, the fact that unilateral nephrectomy is successful in reducing blood pressure in only 20 per cent and probably fewer of the instances in which it has been tried, is certainly poor proof of any hypothesis. The fact that the hypothesis works only 20 per

TABLE VII	
AGE IN SUCCESSFUL UNILATERAL NEPHRECTOMY	
Age in Years	No. of Cases
0-9.....	9
10-19.....	8
20-29.....	6
30-39.....	9
40-49.....	6
50-59.....	5
60-69.....	1
Not stated.....	3
Total.....	47

cent of the time, combined with the astonishing paucity of hypertension in the quoted data on intrarenal pelves, hydronephrosis, tuberculosis and even bilateral pyelonephritis, leaves a lingering doubt that even these forty-seven apparent successes may be fortuitous and failing of demonstra-

tion that the urologic disease was actually the cause of hypertension. As Braasch has suggested in the case of pyelonephritis, renal disease may not produce hypertension in an otherwise normal person, but it may serve as an irritant, somatically and psychically, to bring out latent hypertension or cause exacerbation of an otherwise mild process.

However, as the evidence stands, we are, I think, obliged tentatively to accept these forty-seven patients as "cured." But it would be a most valuable contribution to this problem if those who have reported reduction of blood pressure by nephrectomy would report, at some date in the near future and perhaps for publication in a single issue of an appropriate journal, follow-up studies on all these patients.

In considering the future of this problem, it is worthwhile to state again our requirements for "successful" unilateral nephrectomy. It must first be demonstrated that the patient is truly hypertensive and not simply showing a transiently elevated blood pressure. Second, elevated blood pressure is so labile and so frequently reduced by bed rest or non-specific therapy that little significance can be attached to partial reduction. It is required that the blood pressure be reduced to normal range, i.e., to or below 140/90 and that it remain at this range long enough to exclude non-specific effects. Abeshouse¹ and Goldring, Chasis and myself¹¹³ required one year, while Braasch¹³ and Sensenbach¹⁰⁷ have recommended two years. Perhaps the longer period is the wisest if we are to be certain that we have "cured" the disease.

Braasch¹⁶ estimates that urologic disease is present in no more than 2.5 per cent of hypertensive subjects and that in only one-fifth of these does it present surgical potentialities. This is at best one in 200 persons with hypertension. By rough calculation this would indicate there may be 30,000 persons in the United States who might be aided by unilateral nephrectomy. This is far from therapeutic nihilism and while the internist and psychiatrist settle their differences on the genesis of essential hypertension, the

urologist should search diligently for his potential victories.

But it cannot be emphasized too strongly that, except in rare and well studied instances, the advisability of nephrectomy must rest upon conservative and recognized surgical indications and not upon the hope of reducing blood pressure. In many instances we may expect bilateral renal disease (glomerulonephritis, pyelonephritis, etc.) to be present and it is to be especially noted that hypertensive disease itself is accompanied by a slow, progressive and bilateral destruction of the renal parenchyma,^{47,48} a very important point that is generally overlooked in this problem. To remove one kidney which is supplying perhaps 30 to 40 per cent of the total functional renal tissue available to the patient may well shorten his life. With Sensenbach¹⁰⁷ we emphasize that before removal the diseased kidney should be shown to be essentially functionless and the other kidney free of any evidence of disease.

Even under these conditions there is no certainty of success. May I cite a single instance in which detailed data are available. Weiss and Chasis¹¹⁸ report the results of unilateral nephrectomy in a woman of thirty-four with hypertension of perhaps no more than one and one-half years' duration. Unilateral examination by the clearance methods revealed that the left kidney had negligible glomerular and tubular function, whereas the right kidney showed no evidence of renal disease by the best available methods; on the contrary it was hypertrophic and showed supernormal function in respect to filtration rate, tubular function and blood flow. The left kidney was removed and proved to be an atrophic pyelonephritic kidney weighing 33 Gm. Two months after operation the right kidney was examined again and continued to show supernormal function in respect to filtration rate, blood flow and tubular function. It was practically the equivalent of two normal kidneys. By all criteria this patient was an ideal selection for operation and yet the operation failed to affect her

blood pressure in any way. This example illustrates that it is impossible to know in advance whether the operation will or will not be a "success." The best that can be said is that the operation apparently did her no harm, for the kidney that was removed was functionless, while the remaining kidney was good for the work of two. But in how many cases of nephrectomy are these conditions met? Trousseau's admonition to use the new remedy while it still has the power to heal seems to have found its target in this field. Enthusiasm for nephrectomy appears to be on the wane. I regret that from the enthusiastic phase I have been able to cite only forty-seven cases of the "cure" of hypertension by nephrectomy, and that Braasch's estimate, which is perhaps optimistic, indicates that there are only 30,000 possible candidates for surgical treatment in the entire United States. This figure is a trifling one in comparison with the 15,000,000 adults (i.e., those above twenty-five years of age) who are estimated to have hypertensive disease. A short time ago my colleagues and I calculated from data supplied by the Bureau of the Census that about 1,000,000 persons above the age of forty-five die in this country every year; of this number approximately 450,000, or one out of every two, die of one or another sequela of cardiovascular-renal disease, nearly five times as many as die of cancer. A large fraction of cardiovascular-renal disease is hypertensive in origin, presenting us with what is perhaps medicine's major problem. But if we bring to bear upon this small sector of the battle (unilateral renal hypertension) all the attention and acuity at our command, always adhering to the surgeon's ideals of never to risk shortening a patient's life and never to operate in vain, we may not only multiply this modest number of successes but we may help to pave the way to a better understanding of the disease itself.

SUMMARY

The cause of essential hypertension remains unknown. Despite the large amount

of experimental knowledge available from the Goldblatt experiment, it is not yet demonstrated that the human disease has its origin in either pathologic or functional disturbances of the renal circulation. The data can be interpreted equally well in terms of a generalized and perhaps complex pathologic process which, by arteriolar sclerosis and possibly other mechanisms, attacks the renal parenchyma along with other organs. Although sympathectomy lowers the blood pressure in some instances, it is not yet demonstrated that it changes the temporal progress of the disease.

Pathologically elevated blood pressure is well known to be labile in many persons and susceptible to reduction spontaneously and by prolonged bed rest, psychotherapy and many non-specific agents which have in common only the "enthusiastic treatment of a worried patient." Blood pressure is an unreliable guide to the presence or severity of the disease and more reliable criteria are needed.

Statistical data on blood pressure among the general population indicate that the incidence of essential hypertension, quite low before the age of twenty, increases rapidly thereafter until at the age of forty approximately 25 per cent of the general population are affected, this figure increasing to 60 per cent or more in elderly persons.

There is no convincing evidence that this already high incidence of hypertension is increased by urologic disease (nephrolithiasis, hydronephrosis, prostatic hypertrophy, intrarenal pelvis, nephroptosis, perinephritis, congenital aplasia, pyelonephritis), or, conversely, that the incidence of urologic disease is any greater among hypertensives than among normotensives.

At present the only way a causal relationship between urologic disease and hypertension can be demonstrated in any particular patient is by "curing" the hypertension by removing the offending organ. Because of the lability of pathologically elevated blood pressure, rigid criteria must be observed: i.e., clear demonstration of pre-existing

hypertension, clear demonstration of reduction of blood pressure to normal levels (140/90 or below) and clear demonstration of persistence of pressure at this level for one year or longer. Review of the literature on unilateral nephrectomy reveals that these criteria have apparently been fulfilled in only forty-seven instances out of 242 reported operations.

These forty-seven instances indicate that unilateral renal pathology may be a cause of hypertension in rare instances but the very rarity of success (19 per cent), coupled with the evidence that the bulk of urologic disease does not cause hypertension, still leaves a reasonable doubt about the hypothesis.

The advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure. If bilateral disease is present, and it usually is present in advanced hypertension, as a result of the hypertensive process itself, nephrectomy may shorten life by removing an important fraction of total available renal function.

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The following papers deal with some aspect of the subject matter of this lecture, but in the interests of brevity are not cited in the text: reference numbers 12, 19, 23, 29, 31, 39, 41, 54, 61, 68, 72, 73, 91, 96, 98, 102, 115 and 120.

Seminars on Hypertension

Surgical Treatment of Hypertension*

R. H. SMITHWICK, M.D.

Boston, Massachusetts

SURGICAL treatment of hypertension has been under investigation in a number of clinics during the past twenty years. The three procedures which may be helpful are extensive sympathectomy, unilateral nephrectomy and the removal of adrenal tumors. Extensive sympathectomy is the most widely applicable procedure.

Hypertension, particularly in its later stages, is a complex disorder in which many factors such as the age and sex of the patient, type and the duration of elevated blood pressure and the degree and location of cardiovascular disease vary greatly. While the cause is unknown, there seems to be rather general agreement that elevated blood pressure is the result of increased peripheral resistance to blood flow through the arterioles. Its onset is insidious and in most patients the blood pressure is unusually variable. There is reason to believe that the disorder passes through several stages. The earliest may consist of an unusually variable blood pressure within a normal range, the so-called normotensive hypertactor of Hines and Brown.^{1,2} As years pass by the basal level rises, but it may still be within the usually accepted normal range under resting conditions. On the other hand, blood pressure is usually elevated under conditions of stress and strain or physical activity. This has been called the stage of intermittent hypertension. This stage appears to be tolerated well by most patients, particularly females. In occasional patients, generally males, cardiovascular damage makes its appearance. After a variable period of time, probably many years, the

blood pressure level becomes continually elevated and the upward fluctuations are superimposed. By this time cardiovascular damage is demonstrable in the great majority of patients, in 97 per cent in my experience.³

In the earlier stages of the disorder peripheral resistance is increased intermittently. Later, when blood pressure levels are continually elevated, peripheral resistance is always increased but continues to vary in an upward direction. Cardiovascular disease develops along with hypertension and is progressive. The rate of progress is unpredictable and varies from slow to very rapid. It seems probable that vascular disease is to a large measure the result of increased stress and strain upon the blood vessels. The elevated pressure is in all probability due to increased tone of arteriolar smooth muscle. Vascular disease when present is likely to perpetuate the hypertensive process and prevent the reduction of blood pressure after removal of the physiologic causative mechanisms. For instance, hypertension may be caused by an adrenal tumor. In time vascular disease will develop. The vascular changes may be identical with those in patients having so-called "essential" hypertension. If the changes are sufficiently marked and involve a large vascular area, such as the splanchnic bed, removal of the tumor may have no effect upon the blood pressure. The same is true of patients with continued hypertension of the essential variety. The amount and distribution of vascular disease varies tremendously. Following through denervation of the splanchnic bed, the blood pressure levels may be lowered in a striking fashion

* From The Smithwick Foundation, Massachusetts Memorial Hospitals, Boston, Mass.

in the presence of extensive disease of the renal arterioles in one patient and in another there may be no change at all. The presumption is that in the first patient the peripheral resistance was decreased in the extrarenal visceral vascular bed while in the second, because of vascular disease, it was not modified. The alternate possibility is that some additional factor causing increased tone of smooth muscle existed in the second case, such as a humoral substance acting directly upon smooth muscle.

The three factors which appear to affect peripheral resistance in hypertensive patients are nervous, humoral and vascular disease. Theoretically, all could coexist, and if they were all of equal importance the removal of any one would not affect blood pressure levels. If one is dominant, its removal should be followed by a lowering of the blood pressure level to that at which the others are operating and in their absence to normal.

The mortality in hypertensive patients is due to complications particularly in the cardiac, cerebral and renal areas. That mortality is high is well known and it is believed that there are more deaths per year from hypertensive cardiovascular disease than from any other disorder of mankind. In a recent series of 156 unselected, untreated hypertensive patients who were carefully studied and found to have continued hypertension with evidence of cardiovascular disease varying from slight to marked, we found the mortality to be 26.9 per cent in a follow-up period averaging 5.6 months. These patients had been referred for consideration of surgical treatment and doubtless represented the more severe and advanced forms of the disorder. It is of interest that Bechgaard⁴ recently reported a mortality rate of 28.2 per cent in a series of 1,038 hypertensive patients followed seven to eleven years. This indicates how widely mortality statistics may vary in different series of patients.

As previously indicated, mortality in the earlier stages of hypertension is low because cardiovascular damage of conse-

quence rarely occurs until the stage of continued hypertension is reached. When cardiovascular damage appears in the stage of intermittent hypertension, surgical intervention should be considered. The principal indication for surgery is the presence of continued hypertension with evidence of cardiovascular damage. The purpose is to lower blood pressure levels and to decrease the magnitude of reflex variations in blood pressure by modifying the neurogenic component of peripheral resistance. The rationale is the belief that elevated blood pressure and the associated vasomotor fluctuations accelerate the progress of cardiovascular disease and its fatal complications. The principal contraindications to surgery are the circumstances which we have found from experience to indicate with reasonable certainty that the result of operation will not be worth while. In order to exclude these patients it is necessary to have certain information. This is obtained by subjecting each patient to a standard method of study.

METHOD OF STUDY

An outline of the method of study used is given because the data serve as a basis for dividing subjects into a number of groups. If this information is available, it is then possible to tell whether a given patient falls into the so-called selected or into the excluded group. In general, I would advise those who are beginning to interest themselves in this problem to advise against operation in patients who fall into the excluded group. It is true that some individuals in the selected group will do poorly and some in the excluded group will do well. It is expected that further experience and more detailed studies will make it possible to identify these exceptions with increasing accuracy. Further considerations of this matter are contemplated in the future.

In addition to a detailed history and physical examination, the eyegrounds with fully dilated pupils should be examined by an ophthalmologist. Occasional patients

with continued hypertension have normal eyegrounds. A simple classification has been used which divides the abnormal patients into four grades:

(1) Subjects with spasm only, generalized narrowing or irregular constrictions, or both, of any degree, without evidence of sclerosis and without hemorrhage, exudate or papilledema; (2) sclerotic changes, particularly arteriovenous compression, generally associated with tortuosity and increased light reflex. Spasm may also be present but hemorrhage, exudate and papilledema should not be in evidence; (3) patients with hemorrhage and/or exudate but without papilledema regardless of the changes in the vessels; (4) papilledema with measurable elevation of the disk, generally associated with hemorrhage, exudate and changes of consequence in the retinal arteries.

Cardiac status is determined by a cardiologist, supplemented by an electrocardiogram and a seven foot heart plate with particular reference to the size and shape of the heart and the state of the aorta. The renal area is evaluated by urinalyses, a twelve-hour concentration test and an intravenous phenolsulphonphthalein test (the dye being injected after a period of forced fluid intake and specimens collected at intervals of fifteen and thirty minutes and one and two hours). This ordinary test of renal function has been found useful in estimating the extent of renal damage in hypertensive patients and is the one we have come to rely upon most. A non-protein nitrogen determination is made and intravenous pyelograms are obtained routinely. Blood studies include counts, smears, hemoglobin determinations, blood grouping, Rh factor, Hinton test and determinations of blood sugar, serum protein, cholesterol and chlorides. If a cerebral vascular accident has occurred, a neurologic consultation is requested and such additional studies as skull plates, electroencephalograms and lumbar puncture are carried out as seems indicated.

A postural and cold blood pressure test is

performed as follows: the patient is required to have at least forty-eight hours of bed rest except for lavatory privileges. Following this preliminary period, tests are carried out by technicians rather than by physicians since the former are generally able to obtain lower readings, presumably because physicians often act as a pressor stimulus to the patient. Preliminary readings of blood pressure are taken on each arm. If no great discrepancy exists, the right arm is used. If there is a marked difference on the two sides, this is checked a number of times and the arm with the higher reading is selected. The test is explained to the patient and, after an additional rest period of fifteen to twenty minutes in the horizontal position, observations are begun. It is essential that the environment be quiet, comfortable and pleasant. Ward patients are transported to a special room for performance of the test, during which there should be no interruptions. Readings of pulse and blood pressure are taken every minute for five minutes with the patient lying, sitting and standing. The horizontal position is again assumed and five further readings at minute intervals are taken, following which the opposite hand is immersed in ice water (4° to 5°C.) up to the wrist for exactly one minute and readings are taken after thirty seconds and at the end of the sixty seconds of stimulation by cold. Readings are then continued at one-minute intervals for an additional five minutes. The patient then assumes the upright position and after five preliminary readings at one-minute intervals the cold stimulus is repeated exactly as in the horizontal position.

The average of the five readings in the horizontal position in the first portion of the test is called the resting blood pressure level and is used to divide patients into three types, the purpose of which is to arrange them into similar categories according to the width of the pulse pressure in the resting horizontal position. In general, in both males and females the wider the pulse pressure the poorer the statistical

chances for lowering the blood pressure. In type I, the pulse pressure is less than one-half the diastolic pressure. In type II, the pulse pressure is equal to or up to 19 mm. more than one-half the diastolic pressure. In type III, the pulse pressure is 20 mm. or more greater than one-half the diastolic pressure.

A sedative test is performed in all patients. Following a light supper, three grains of sodium amytal are given by mouth at 6:00, 7:00 and at 8:00 P.M. Hourly readings of pulse and blood pressure are recorded from 7:00 P.M. to 7:00 A.M. The lowest reading of systolic and diastolic blood pressure is taken as the response. This is evaluated by comparison with the horizontal or resting blood pressure level as determined by the postural and cold test and the diastolic response is regarded as the most significant figure. For patients with resting diastolic levels in the postural and cold test below 120 mm., the diastolic response to sedation should be to 90 or less; for those in the range of 120 to 129 mm., it should be to 100 or less; and for those with resting levels of 130 mm. or more it should be to 110 mm. or less in order to be regarded as satisfactory. Better responses than this not infrequently occur and are regarded as good or excellent. A lesser response also is not uncommon and is regarded as poor.

SELECTION OF CASES FOR SURGERY

With the above information it is possible to determine whether a patient falls into the selected or the excluded group. An individual may be regarded as being in the latter category if any of the circumstances under which the results of operation are most likely to be unsatisfactory apply. These determining circumstances are divided into two groups, A, general, and B, more specific. The latter were compiled by dividing the patients into twelve groups according to age, i.e., below forty and forty and over, and two sexes and three types. The resting diastolic level, the state of the brain, eyegrounds, heart and kidneys, as well as

the response to sedation, were also taken into consideration.

The circumstances under which operation has been found most likely to be unsuccessful are as follows:

A. (1) When nitrogen retention is present; (2) when actual or impending congestive heart failure is associated with poor kidney function (intravenous phenolsulphonphthalein output less than 15 per cent in fifteen minutes and 50 per cent in two hours); (3) when renal function is poor but the cardiac status satisfactory if the patient has had a cerebral vascular accident or has grade (3) or (4) eyeground changes. Possible exceptions are subjects with known pyelonephritis or an unusually marked response to sedation or both; (4) when the cardiac changes are marked (actual or impending congestive heart failure) and the renal function is satisfactory (intravenous phenolsulphonphthalein output 15 per cent in fifteen minutes and 50 per cent or more in two hours) in the presence of a cerebral vascular accident or grade (3) or (4) eyeground changes. Possible exceptions are patients with known pyelonephritis or a remarkable response to sedation or both. Operation may be considered if the renal function is normal and the response to sedation satisfactory. The heart, however, must be well compensated and must have responded well to medical measures.

B. If the preceding circumstances do not apply to a particular patient the following criteria should also be considered before advising surgical treatment:

1. Type I Males. If the resting diastolic level is less than 120, operation may be performed if the general suggestions do not apply. For diastolic levels 120 to 130, age thirty-eight or more, it has been noted that these patients who have had a cerebral vascular accident or have grade (3) or (4) eyeground changes have done poorly unless the response to sedation is satisfactory and the electrocardiogram or renal function is normal (intravenous phenolsulphonphthalein output 25 per cent in fifteen minutes and 50 per cent or more in two hours).

If either the electrocardiogram or kidney function is abnormal, the changes should be slight at most. When the resting diastolic level is 140 mm. or more, the outlook is poor in general. Operation in these individuals seems inadvisable if there has been a cerebral vascular accident, encephalopathy, congestive heart failure, or more than slight impairment of renal function (intravenous phenolsulphonphthalein output 20 per cent in fifteen minutes and 50 per cent or more in two hours). If the patient has grade (2), (3) or (4) eyeground changes, the electrocardiogram should be normal. If the eyegrounds are normal or grade (1), operation may be performed if the cardiac and renal changes are slight at most.

2. Type I Females. If the resting diastolic level is below 120, operation may be performed if the general suggestions do not apply. If the resting diastolic level is 120 or more and the patient has had a cerebral accident, encephalopathy or has grade (3) or (4) eyeground changes, operation may be performed if the cardiac and renal functions and the response to sedation are satisfactory. If the response to sedation is poor and the patient is under thirty-eight years of age, the result may be worth while if the electrocardiogram is normal or chronic pyelonephritis is known to exist.

3. Type II Males. Patients under forty years of age to whom the general suggestions do not apply, have done poorly when the resting diastolic level is below 110 mm. and grade (3) eyeground changes are present. Male patients in this same age group with resting diastolic levels of 130 mm or more have done poorly unless the changes in all areas are minimal at most. Male patients type II, age forty and over, have done poorly at all diastolic levels if the response to sedation is poor. Also, if the response to sedation is satisfactory and the resting diastolic level is 120 mm. or more, the results have been poor when renal function has been poor (intravenous phenolsulphonphthalein output of less than 15 per cent in fifteen minutes and 50 per cent in two

hours). If the response to sedation is satisfactory and the resting diastolic level is 120 mm. or more and the eyegrounds are grade (3), the results have been poor unless renal function is good (intravenous phenolsulphonphthalein output 20 per cent in fifteen minutes and 50 per cent or more in two hours).

4. Type II Females. Below the age of forty these patients have done unusually well when the general suggestions do not apply. Patients age forty and over to whom the general suggestions do not apply have not done well if there has been a cerebral accident and the eyegrounds are grade (3) or (4). Also type II females, age forty-five and over, have in the great majority of instances done poorly if the response to sedation is unsatisfactory.

5. Type III Males. Below the age of forty operation may be performed if the general rules do not apply except in patients with eyeground changes greater than normal or grade (1), unless the renal function is normal (intravenous phenolsulphonphthalein output 25 per cent in fifteen minutes and 50 per cent or more in two hours). Patients age forty and over have done poorly if the response to sedation is poor. Patients age forty-five and over with grade (3) eyegrounds and abnormal electrocardiograms have done poorly when the renal changes are more than slight (intravenous phenolsulphonphthalein output less than 20 per cent in fifteen minutes and 50 per cent in two hours).

6. Type III Females. Below the age of forty these patients have done unusually well if the general suggestions do not apply. If the age is forty or over, patients who have had a cerebral accident have done poorly unless the eyegrounds are normal or grade (1) and the diastolic response to sedation is to below 80. Patients age forty and over with resting diastolic levels of 130 mm. or more have done poorly.

EARLY RESULTS

In a group of 439 patients with continued hypertension and slight to marked cardio-

vascular changes, these rules were found to apply to 120 of the patients and were found not to apply to 319 subjects. These patients were followed by the author and associates for a period of from one to five or more years. The results in each group are shown

TABLE I*

A SERIES OF 439 UNSELECTED PATIENTS WHO HAVE BEEN OPERATED UPON AND FOLLOWED FOR ONE TO FIVE OR MORE YEARS
Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	22 8	14 5	28 9	6 6	5 8	6 8	14 6
Total (per cent)	66 2			12 4			

Cardiovascular Disease							
	Improved		Unchanged	Equivocal		Worse	
Per cent	A 61 7		B 10 0	C 9 2		D 19 1	

* These patients have been divided into two groups in Tables II and III, the so-called excluded and selected cases.

in Tables I, II and III, respectively. The results have been judged both by the effect upon blood pressure and the effect on cardiovascular disease.

The effect upon blood pressure is tabulated as improved, unchanged, higher and deaths. The effect upon cardiovascular disease has been tabulated as improved, unchanged, equivocal or worse. The effect upon blood pressure was divided into seven categories which are as follows: (1) diastolic pressure lowered 20 mm. or more, and to below 90; (2) diastolic pressure lowered 20 mm. or more, but not to below 90; (3) diastolic pressure lowered less than 20 mm. to no change at all, pulse pressure definitely narrowed and ceiling levels lowered; (4) diastolic level and pulse pressure essentially unchanged but ceiling levels lowered; (5) no change in blood pressure; (6) blood pressure higher and (7) deaths.

Blood pressure changes graded as 1, 2 or 3 comprise the improved group; those graded

4 and 5, unchanged; those graded 6, higher; those graded 7 include the deaths.

The effect upon cardiovascular disease has been graded as follows: A, this group contains subjects with favorable changes in one or all areas with no evidence of progress

TABLE II

SERIES OF 120 PATIENTS HAVING CONTINUED HYPERTENSION AND CARDIOVASCULAR CHANGES WHO HAVE BEEN OPERATED ON AND FOLLOWED FROM ONE TO FIVE OR MORE YEARS AND WHO WOULD BE EXCLUDED

BY THE RULES
Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	2 5	5 8	7 5	7 5	8 3	16 7	51 7
Total (per cent)	15 8			15 8			
Cardiovascular Disease							
	Improved		Unchanged	Equivocal		Worse	
Per cent	A 23 3		B 6 7	C 10 8		D 59 2	

TABLE III

SERIES OF 319 PATIENTS HAVING CONTINUED HYPERTENSION AND CARDIOVASCULAR CHANGES WHO HAVE BEEN OPERATED ON AND FOLLOWED ONE TO FIVE OR MORE YEARS TO WHOM THE RULES DO NOT APPLY AND WHO WOULD NOT BE EXCLUDED

BY THEM
Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	30 1	17 6	37 1	6 2	5 4	2 4	1 2
Total (per cent)	84 8			11 6			

Cardiovascular Disease				
	Improved	Unchanged	Lquivocal	Worse
Per cent	A 76 2	B 11 3	C 8 5	D 4 0

in any area. B, in this group are subjects in which there is no evidence of reversal or improvement in any area but also no evi-

dence of progression. c, in this group fall subjects in which there is evidence of improvement in one or more areas but also evidence of progress of cardiovascular disease in another or other areas. d, these subjects show no evidence of improvement

TABLE IV
SURGICAL TREATMENT OF HYPERTENSION
Early Results of Sympathectomy and Splanchnicectomy
by Various Technics in Patients Followed
from Months to Five Years or More

Author	No. Cases	Subjective and Objective Improvement	Subjective Improvement, No change, or Worse	Deaths
		(per cent)	(per cent)	(per cent)
Allen and Adson ³ (1940)	224	31.0	53.8	15.2
Peet, Woods, Braden ⁶ (1940)	350	42.6	26.8	30.6
Hammarström ⁷ (1947)	82	54.9	18.2	26.9
Smithwick ³ (1947)	439	61.7	23.7	14.6
Poppen and Lemmon ⁸ (1947)	100	71.0	22.0	7.0
Grimson ⁹ (1946)	41	76.0	6.3	17.7

Late Results of Supradiaphragmatic Splanchnicectomy
in Patients Followed for Five to Twelve Years

Peet ¹⁰ (1946)	437	46.7	8.1	42.5
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or no change in one or more areas associated with evidence of progression in one or more areas. Deaths are also placed in this group.

Subjects graded as A are tabulated as improved; B, unchanged; C, equivocal; D, worse.

In Table IV, the early results of sympathectomy and splanchnicectomy by various technics^{3,5-10} are summarized. These appear to me to be representative reports from the literature. I have taken the liberty of arranging the results under certain headings and estimating the percentages from the data appearing in the articles. This was necessary because no standard method of reporting results has been used. I believe the general impression of the results as judged by the various authors themselves has not been materially altered. Only one report of late results in a large series of cases has so far appeared in the literature. This report by Peet¹⁰ is also summarized in Table IV.

We believe that these results are poor and that the statistical chances for improvement are not great enough to justify surgery in patients falling into this category.

We believe the results in this series are much better and for the most part seem worth while for the period of observation. These results are approximately what one may anticipate if patients are operated upon who are not excluded by the rules. The majority of these patients have been followed for less than three years. A longer follow-up will no doubt reveal that operation was not worth while in some of them. A follow-up study of patients operated upon five or more years ago is now in progress. This should give a more accurate idea of the long range outlook for surgically treated patients. It is hoped that these data will make it possible to establish criteria which will insure a satisfactory late result in a high percentage of patients.

PHYSIOLOGIC EFFECT OF EXTENSIVE SYMPH-ECTOMY UPON BLOOD PRESSURE LEVELS AND VASOMOTOR RESPONSES

In the patients referred to in Tables I, II and III, the operation performed was lumbo-dorsal (thoracolumbar) splanchnicectomy. The minimal procedure should be the removal of the sympathetic trunks bilaterally from D₈ to L₁ inclusive. The great splanchnic nerves are removed from the celiac ganglia to the mid-thoracic level. In some subjects resection of the trunks was more extensive. We are not certain that more extensive resections are more effective. The operation is performed in two stages spaced ten days apart. This operation fulfills certain criteria which we believe to be important: (1) minimal operative mortality and morbidity; (2) maximal possibilities for blood pressure reduction; (3) maximal reduction of reflex variations in blood pressure; (4) maximal protection against regeneration; (5) absence of serious untoward effects; (6) provision for exploration of adrenal glands and adequate exposure for the removal of tumors; and (7) provision

for inspection and biopsy of kidneys and exposure for nephrectomy if indicated.

During the last year or two, we have performed subtotal to total thoracic sympathectomy in two groups of patients and believe that these procedures may prove to be preferable to lumbodorsal splanchnicectomy under certain circumstances. First are patients with hypertensive cardiovascular disease with angina pectoris. In these the sympathetic trunks were removed bilaterally from the inferior cervical to the twelfth thoracic ganglia inclusive, together with the splanchnic nerves arising from these segments. Second is a group of patients with hypertensive cardiovascular disease and unusual tachycardia. In these the trunks were removed from the second to the twelfth thoracic ganglia. The operations were performed in two stages about two weeks apart. The results in these patients will be reported at a later date. They are mentioned at this time because the physiologic effect seems comparable, quantitatively speaking, to that following lumbodorsal splanchnicectomy, particularly as regards modification of vasomotor responses.

Two physiologic effects of extensive sympathectomy upon blood pressure are (1) changes in levels and (2) modification of vasomotor responses. These consist of a lowering of diastolic pressure, a narrowing of the pulse pressure and reduction of ceiling levels following stimulation. Reference to Table 1 indicates the percentage of unselected subjects having these various modifications of blood pressure levels. It will be noted that a grade (1) effect was obtained in 22.8 per cent of the patients. The blood pressure levels of 100 hypertensive patients who obtained grade (1) results compared favorably with those of a control series of 100 normotensive patients studied in the same fashion. The hypertension was largely reversible in these patients, suggesting that increased peripheral resistance to blood flow in certain hypertensive patients can be markedly decreased by splanchnicectomy. (Fig. 1.) Two subjects with grade (1) results are illustrated in Figures 2 and 3;

these are typical examples of patients ideally suited for surgical treatment. A poor candidate for surgery is illustrated in Figure 4.

Modification of vasomotor responses has been regularly observed by Wilkins and Culbertson^{11,12} in response to various stimuli following lumbodorsal or total thoracic sympathectomy. The same is true after total sympathectomy. These responses are not abolished after lesser maneuvers such as subdiaphragmatic or supradiaphragmatic splanchnicectomy. Following lumbodorsal or total thoracic sympathectomy, vasomotor responses following the Valsalva maneuver are almost always completely abolished. (Fig. 5.) It seems probable that reversal of cardiovascular damage existing prior to operation is due in part to decreased stress and strain upon the vascular bed resulting from modification of reflex vasomotor variations in blood pressure. This physiologic effect together with lowering of blood pressure levels are probably the two most important changes after extensive sympathectomy. Other possible effects, such as elimination of reflex secretion of adrenalin, decreased production of sympathin and the stabilization of blood flow through the denervated area, are perhaps of lesser importance. Favorable changes in eyegrounds, electrocardiograms, heart size and renal function as judged by ordinary tests have been described in other communications.¹³⁻¹⁷

UNTOWARD EFFECTS OF EXTENSIVE SYMPATHECTOMY

Following extensive sympathectomy, certain undesirable effects are noted. The denervated areas do not perspire, consequently sweating is increased in the undenervated areas. Also, vasomotor responses are abolished in denervated areas and increased in undenervated regions. Consequently, excessive perspiration in the upper portion of the body and cold hands are commonly noted after lumbodorsal or thoracolumbar splanchnicectomy. The same changes are noted in the lower extremities after total thoracic sympathectomy. These

effects are unpleasant but not serious and decrease with the passage of time. Postural hypotension with tachycardia is present after lumbodorsal splanchnicectomy and without tachycardia after total or subtotal thoracic sympathectomy. Leg bandages or elastic stockings and a lower abdominal

the heart at a later date to abolish this difficulty. In retrospect, both patients had unusual tachycardia prior to operation and in such patients we now include cardiac denervation as part of the original maneuver.

Abolition of ejaculation regularly follows extensive removal of the lumbar outflow. If

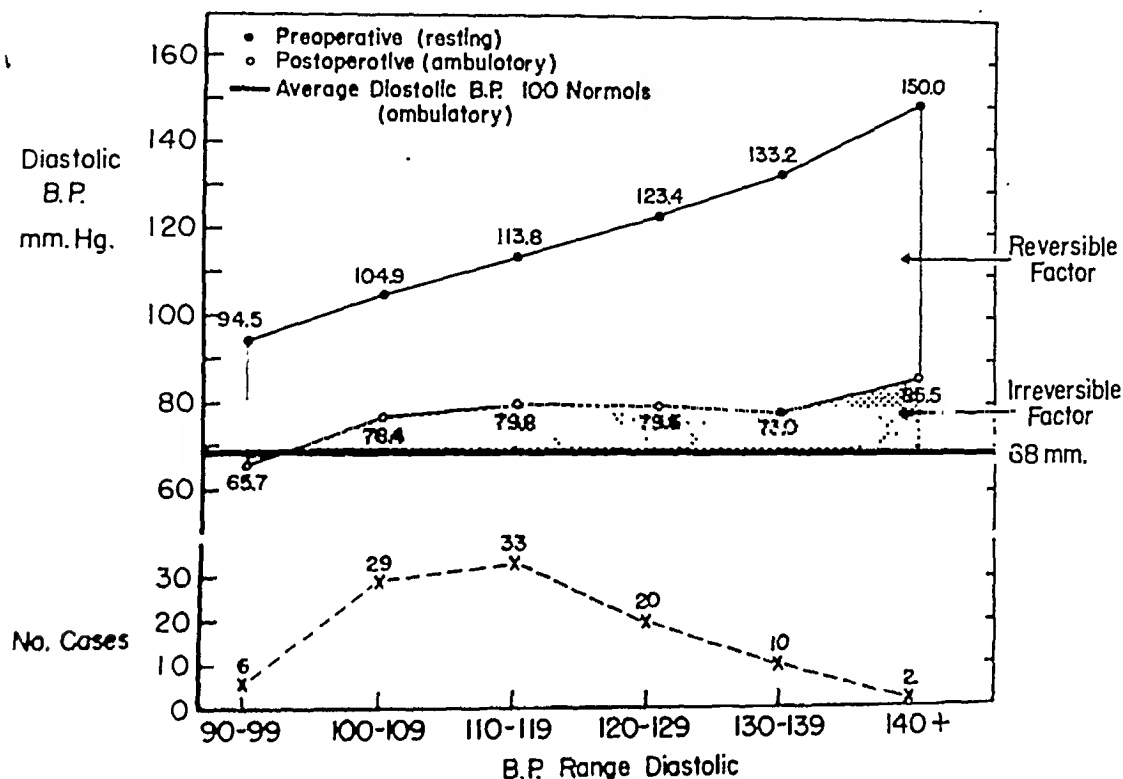


FIG. 1. In this chart the preoperative diastolic pressures are compared with the postoperative levels in one hundred patients who obtained a grade 1 result. Preoperative levels were determined after forty-eight hours of bed rest; postoperative levels were ambulatory and were obtained after fifteen or twenty minutes' rest in a horizontal position. The patients are divided into groups according to the height of the preoperative diastolic levels. The levels for all patients with pressures falling within each 10 mm. range were averaged. The average of the postoperative values for these same patients are charted immediately beneath. A base line of 68 mm. of mercury is used for comparison since this was found to be the average diastolic level of one hundred normotensive individuals studied in an ambulatory fashion by technicians after fifteen or twenty minutes' rest. The chart indicates that in these patients the hypertension was largely reversible at all diastolic levels. This suggests that in certain patients with continued hypertension the nervous system may be largely responsible for the increased tone of arteriolar smooth muscle. Examples of grade 1 results are illustrated in Figures 2 and 3.

girdle are used to counteract these effects in the early postoperative period. These changes gradually disappear after four to six months in the great majority of patients. The basal pulse rate is slower after both procedures, markedly so after total and subtotal thoracic sympathectomy. In an occasional patient, tachycardia in response to exercise persists to a troublesome degree after lumbodorsal splanchnicectomy. In two patients it was necessary to denervate

both first lumbar ganglia only are removed, ejaculation is preserved in the great majority of individuals. If preservation of this function is imperative, the lumbar outflow on one side should be left intact. Orgasm is not affected. Impotence is rare after operations of any magnitude. It is difficult to explain its occurrence on a physiologic basis since erection is mediated by the parasympathetic division of the autonomic nervous system.

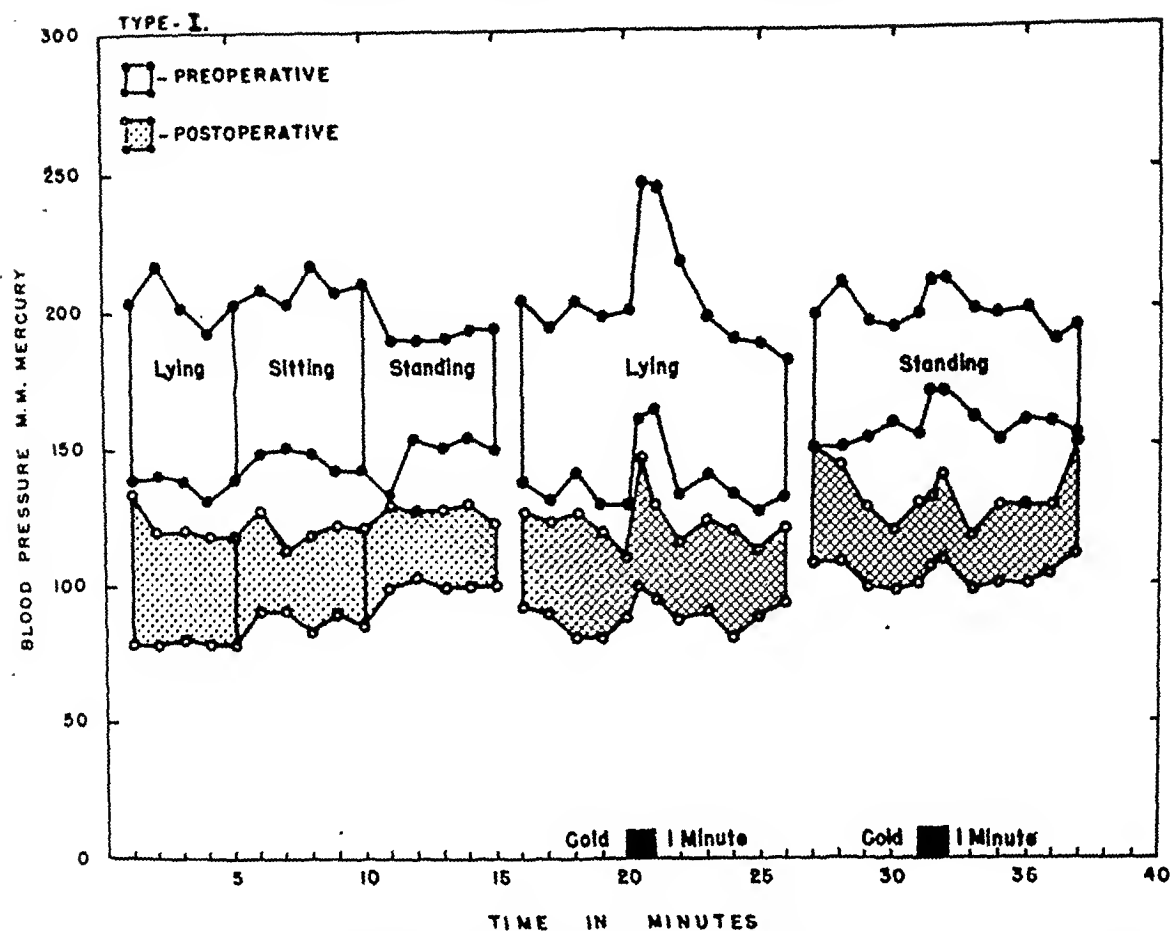


FIG. 2. This twenty-nine year old patient first knew of her hypertension two and one-half years prior to operation. It developed during the sixth month of her first and only pregnancy and was associated with severe toxemia necessitating termination of the pregnancy. The fetus was not viable. Since that time, hypertension persisted and remained severe. This was associated with frequent severe headaches. Various therapeutic measures were ineffective, including x-ray treatment of the pituitary. The retinal arteries were diffusely narrowed and irregular and there was some increased tortuosity. There were scattered exudates; the electrocardiogram was normal and the heart was slightly enlarged and the aorta tortuous. Renal function was satisfactory by ordinary tests, with persistent albuminuria. On sedation the blood pressure fell to 126/84. The blood pressure levels before and thirteen months after operation were as follows:

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting)	196/132	194/147	230/172	230/170	30/34	54/30
Postoperative (ambulatory)	122/78	128/100	146/100	138/108	34/12	8/8

Examination of the cardiovascular system revealed normal eyegrounds, normal electrocardiogram, normal heart size and normal renal function. The patient is extremely anxious to have a child and was told that in view of previous experiences with pregnancy, following a good response to operation that it would be safe for her to have a further trial of pregnancy.

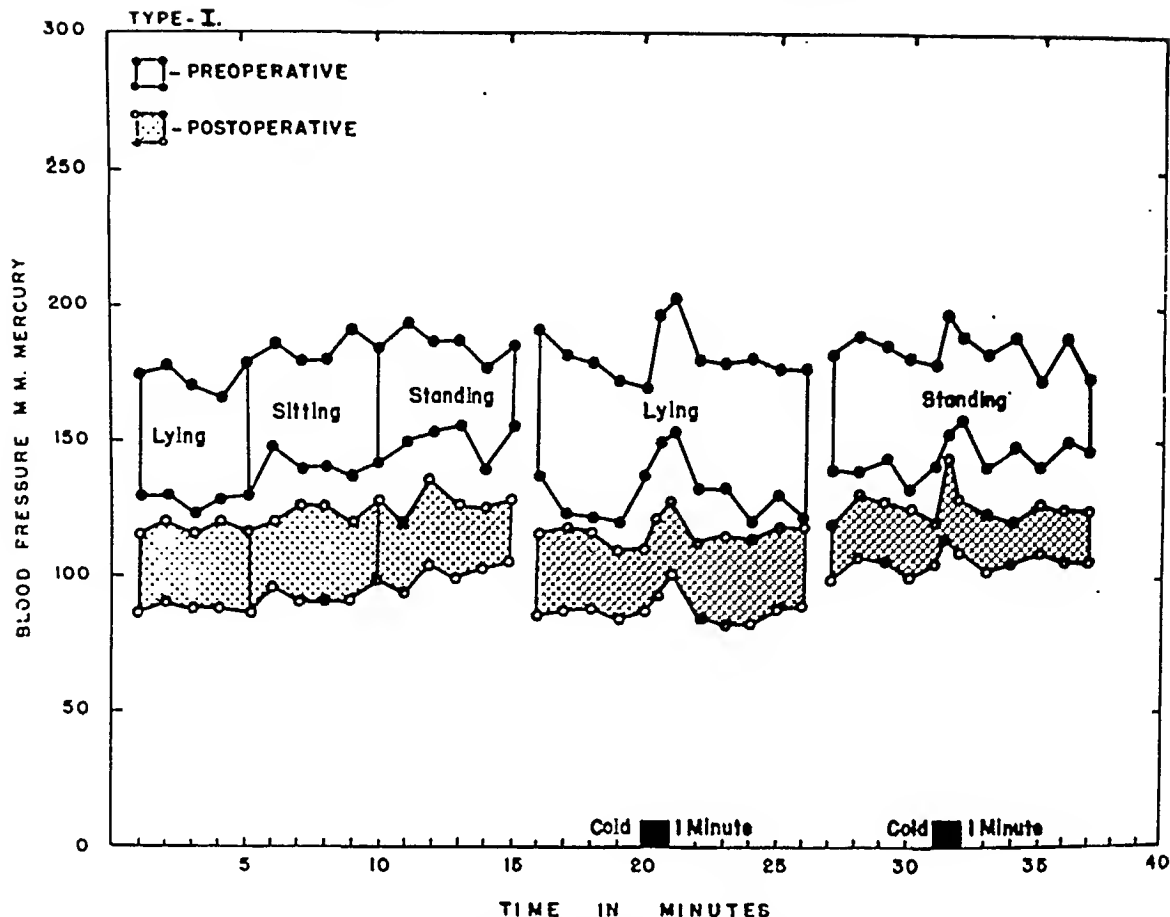


FIG. 3. This thirty-six year old police officer was found to have severe hypertension with eyeground changes which consisted of marked beading and irregular constrictions of the retinal arteries with scattered hemorrhages and one diopter of papilledema. So far as he knew the hypertension was of less than one year's duration. Occipital headaches in the morning and ease of fatigue were the principal symptoms. Aside from the eyegrounds and early electrocardiographic changes, the cerebral, cardiac and renal areas were apparently normal. His blood pressure fell to 130/90 on sedation. His blood pressure levels before and at intervals after operation are tabulated. Those before and five years after operation are illustrated as follows:

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting)	175/120	189/152	204/154	198/160	36/16	18/18
Postoperative (ambulatory) (12 mo.)	127/90	132/105	124/104	150/118	-10/+10	12/10
(41 mo.)	113/80	128/94	110/90	124/94	0/12	4/6
(60 mo.)	118/86	128/102	130/102	144/116	18/14	20/10

It is of interest that the renal biopsy material revealed very advanced chronic vascular nephritis, grade 4. This patient, as well as the patient illustrated by Figure 2, are the best candidates for surgery. They have the following features in common which are indicative of a worth while result: narrow pulse pressure (types I and II), younger age group, variable hypertension with hyper-reactivity, not too severe cardiovascular damage and a good response to sedation.

PREGNANCY FOLLOWING LUMBODORSAL
SPLANCHNICECTOMY

An increasing number of patients are being permitted to attempt pregnancy

degrees of cardiovascular damage prior to splanchnicectomy. Approximately half of the patients had chronic pyelonephritis. Three patients had malignant hypertension.

TYPE - III

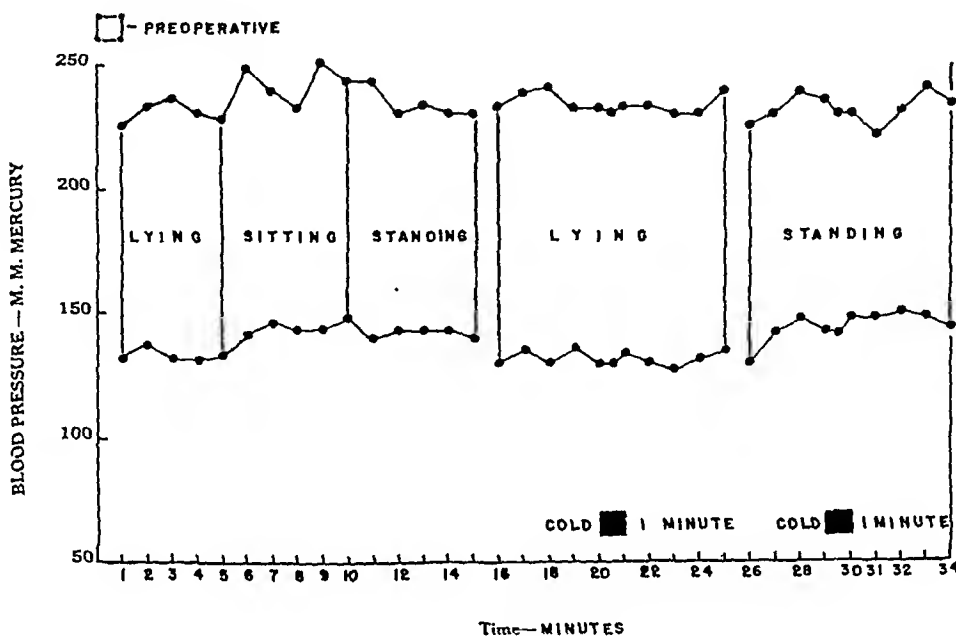


FIG. 4. This thirty-nine year old female patient is illustrative of some of the circumstances under which operation is most likely to fail to modify the hypertensive state. About six months prior to admission she suffered a cerebral vascular accident from which she had recovered satisfactorily without much residual. Her eyegrounds showed marked changes in the arteries with hemorrhages, exudate and papilledema. Her heart was enlarged and she had early congestive failure. The electrocardiogram was abnormal. Her renal function was markedly impaired as judged by ordinary tests. The non-protein nitrogen was within normal limits. There was no response to sedation. The blood pressure levels as determined by the postural and cold test after a period of bed rest are illustrated and were high and fixed. The pulse pressure was wide (type m).

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting) . .	230/134	236/142	234/134	230/148	2/4	-6/+4

This patient was operated upon and died within a year of a recurrent cerebral accident. There was no change in her blood pressure levels after operation. From experiences of this sort we have learned that patients who fall into certain categories are poor candidates for surgery and should be excluded. Many patients of this sort are in Table II and are commented upon in greater detail in the text.

following a favorable response to extensive sympathectomy. The course of pregnancy in fourteen patients was recently discussed by Newell and Smithwick.¹⁸ These patients had continued hypertension with varying

The time elapsing between the diagnosis of hypertension and operation averaged seventy-five months. The time between operation and pregnancy averaged thirty months with the exception of one woman

on whom splanchnicectomy was performed during the first trimester. Admission blood pressure levels prior to splanchnicectomy averaged 196/130, prior to pregnancy 135/87, two weeks post partum 134/89, and six or more weeks post partum 133/87. All

elevation of blood pressure varying from slight to marked necessitated termination of the pregnancy. All obtained living children as this complication occurred late in pregnancy. The series has increased considerably. Two additional patients having

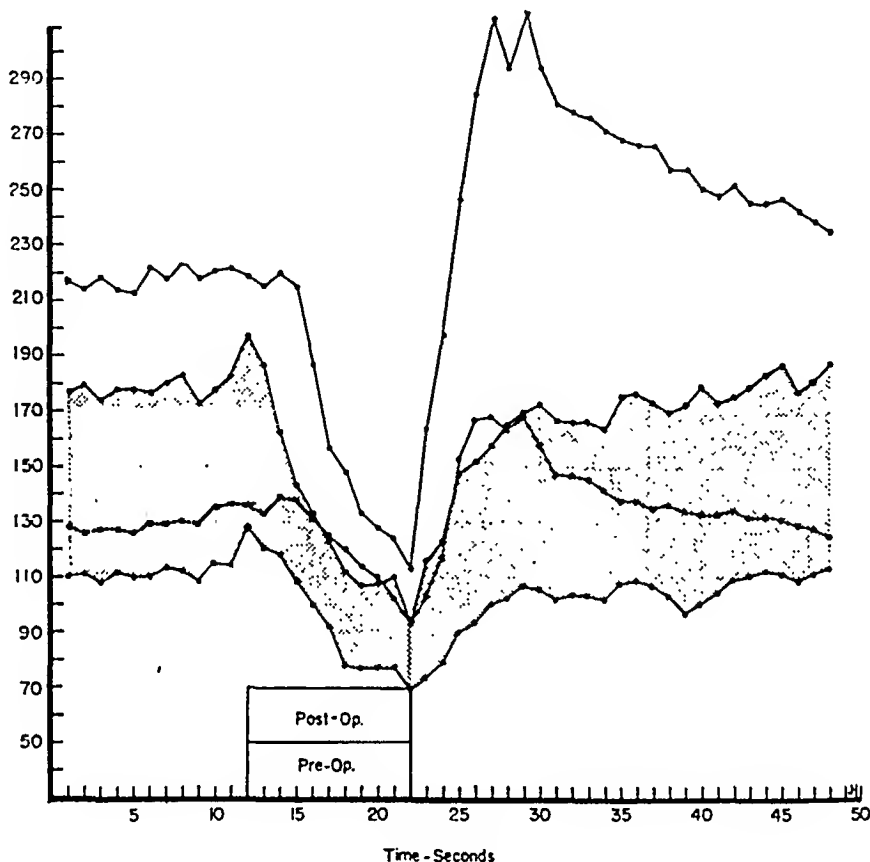


FIG. 5. This is a typical example of the modification of reflex vasomotor variations in blood pressure following thorough denervation of the splanchnic bed. Intra-arterial blood pressure levels are optically recorded with a Hamilton manometer before, during and after the Valsalva maneuver. The latter consists of exhaling against a positive pressure of about 40 mm. of mercury for ten seconds which causes a sharp fall in blood pressure. The sharp overshoot which follows within a few seconds before operation is compared with the abolition of this phenomenon after operation (shaded graph). This indicates that denervation of a large vascular area minimizes reflex vasomotor variations in blood pressure. This should decrease stress and strain upon the vascular bed. This physiologic effect of sympathectomy occurs in all thoroughly denervated patients and is unrelated to changes in blood pressure levels.

but one patient obtained a living child and did not appear to have suffered cardiovascular damage. One still birth resulted from premature separation of the placenta. This patient subsequently obtained a living child at a second pregnancy. In nine women the pregnancy was entirely uneventful without elevation of blood pressure or signs of toxemia. In five, signs of toxemia with

severe continued hypertension were operated upon in the first trimester and delivered uneventfully at term. Several other patients, one with large bilateral polycystic kidneys, have become pregnant at various time intervals after operation and all have had an uneventful course and obtained living babies. It is our impression that following a satisfactory response to opera-

tion, pregnancy, if carefully supervised, appears to be safe and permissible. These experiences lead us to believe that following this operation certain hypertensive women may be able to tolerate pregnancy which would otherwise be impossible or extremely hazardous. This is particularly true in the younger age group with severe essential and even malignant hypertension, with or without chronic pyelonephritis.

UNILATERAL NEPHRECTOMY

The removal of one kidney in hypertensive patients should be undertaken with caution. The number of hypertensive patients who might benefit from such a procedure is small and is thought to be less than 1 per cent of all. Opinions vary as to the rationale for this procedure. It is based upon the experimental work of Goldblatt who demonstrated clearly that transient hypertension follows partial clamping of one renal artery in dogs. More persistent hypertension can be produced in other animals in this way, particularly in rats. If the clamp or the kidney is removed, the hypertension disappears.

A critical analysis of the results of unilateral nephrectomy by Goldring and Chasis¹⁹ led them to believe that 10 per cent of patients so treated were improved. Two recent reports by Ratliff et al.²⁰ and Barker and Braasch²¹ are more optimistic. They indicate that moderate improvement lasting for years may be expected in about one-third of the patients and slight improvement in an additional 15 per cent. It should be emphasized that only seriously affected or non-functioning kidneys should be removed. The function of the remaining kidney should be little if at all impaired. It seems inadvisable to remove the poorer of two involved kidneys. In general, the indications for nephrectomy in hypertensive patients should be essentially the same as in non-hypertensive patients. Unilateral nephrectomy may be combined with lumbodorsal splanchnicectomy providing infection does not contraindicate such a procedure.

ADRENAL TUMORS AND PARAGANGLIOMAS

Adrenal tumors have been present in about 4 per cent of the hypertensive patients operated upon by the author. About 90 per cent of these are cortical adenomas and their relation to the hypertensive state is not as yet clear. Only one of these was clearly an important factor. Ten per cent of the tumors have been pheochromocytomas and with one exception they have been physiologically active. Ninety per cent of these patients have a definite history of paroxysmal attacks of hypertension associated most commonly with headache, palpitation, vomiting and sweating. Ten per cent have no such symptoms. To confuse the issue further, adrenal tumors have been more commonly absent than present in paroxysmal forms of hypertension in my experience. While there are other suggestive findings such as hypermetabolism, hyperglycemia, an active pressor response to histamine or acetylcholine, a normal or decreased response to stimulation by cold or postural hypotension associated with tachycardia, none of these signs is absolutely diagnostic. In some instances a tumor can be felt but this is rare in my experience. An attack may be precipitated by massage, straining or emotion. The diagnosis may be suggested by intravenous pyelography or perirenal air injection. The latter is not without danger. The only certain and safe way to make the diagnosis is to explore the adrenal glands. As previously stated, this should be a part of any widely utilized operation in hypertensive patients. It is important that the diagnosis be made since the effect of removing physiologically active tumors is almost always dramatic. It is unfortunate that the diagnosis has so far been made most frequently at autopsy.

SUMMARY

There are three surgical measures which may be helpful in the management of hypertensive patients.

Unilateral nephrectomy appears to have modified the course of the disorder in some

patients. It appears to be difficult or impossible to predict the outcome. It seems permissible to remove a seriously damaged or non-functioning kidney when the other is little if at all affected. It seems unwise to remove the poorer of two involved kidneys. In general, the indications for nephrectomy should be the same in hypertensive as in non-hypertensive patients.

The removal of adrenal tumors which are physiologically active is helpful. In those patients having paroxysmal hypertension the diagnosis can often be made with considerable certainty. On the other hand, paroxysmal forms of hypertension may not be due to tumors but appear to be the result of an intermittent increase in diencephalic activity. In these patients denervation of the splanchnic bed has been effective. Continued non-paroxysmal hypertension may be caused by an adrenal tumor. The diagnosis may be difficult to make and most of these tumors have been found unexpectedly during the course of operations upon the sympathetic nervous system. In general, active adrenal tumors are rare causes of hypertension. They almost always prove to be pheochromocytomas.

Surgical intervention upon the sympathetic nervous system appears to offer many patients a reasonable chance for improvement at a minimal risk. It appears to slow the progress of the disorder. It probably is rarely if ever curative. A lessening of the severity of cardiovascular damage, as judged by favorable changes in the retinal, cardiac or renal areas, was noted in about 60 per cent of unselected patients followed from one to five or more years. Blood pressure levels were also modified slightly to markedly in about 60 per cent of these subjects. It is believed that at least part of the effect of the operation is due to a modification of reflex vasomotor fluctuations in blood pressure. This effect is independent of changes in blood pressure levels and occurs in virtually all thoroughly denervated patients. It is possible that elimination of reflex secretion of adrenalin and a stabilization of

blood flow through the denervated area may be of some importance.

Extensive sympathectomy has been utilized largely in patients who have reached the stage of continued hypertension with evidence of cardiovascular damage varying from slight to marked. Experience to date indicates that at least 30 per cent of these patients are clearly unsuited for this form of treatment and rules have been formulated in an attempt to exclude them as far as possible. If such patients are excluded, the early results in the remaining subjects are considerably better. A follow-up period of five years or more is needed to establish the circumstances under which splanchnicectomy is most likely to be worth while. It is gradually becoming apparent that patients with the best chance for good results are those in the younger age groups with narrower pulse pressures, (types 1 and 2) with variable blood pressures, the cardiovascular systems not too extensively damaged and with satisfactory responses to sedation. Two typical examples of patients ideally suited for surgical treatment are illustrated in Figures 2 and 3. A poor candidate for surgery is illustrated in Figure 4.

Occasional patients develop evidence of cardiovascular damage in the stage of intermittent hypertension. In these it seems proper to consider surgical intervention. Thorough denervation of the splanchnic bed by a technic which permits exposure of the kidneys and adrenal glands appears to be the most desirable procedure for most patients. In some, total or subtotal thoracic sympathectomy may prove to be preferable.

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Nephrotic Syndrome Occurring during Tridione Therapy*

HENRY L. BARNETT, M.D., DONALD J. SIMONS, M.D. and ROE E. WELLS, JR., M.D.
New York, New York

A RELATIVELY new drug, tridione (3, 5, 5 trimethyloxazolidine, 2-4 dione) has been shown to possess high therapeutic specificity against petit mal seizures.¹ The rare occurrence of serious toxic side effects has also been reported recently.² This report concerns a hitherto undescribed renal complication which appears to be related to the administration of tridione.

CASE REPORT

A sixteen year old colored school girl (born April 15, 1931) was first seen at seven and one-half years of age in January, 1939 in the out-patient department of the Children's Clinic of the New York Hospital. The initial complaint was enuresis of one year's duration. Subsequently, her mother described "spells" during which she seemed to be "thinking like dreaming" and as a result stopped whatever she was doing. She became rigid, stared and did not respond to questioning. These episodes lasted about thirty seconds and had been noted for about three months.

No other members of the family were known to have had convulsive disorders or kidney disease. The mother had syphilis and was treated during the pregnancy of the patient.

Physical examination of the patient was unremarkable. She appeared dull and slow. Her intelligence quotient at the age of eight years was 83. Re-examination at the age of eleven, however, cast doubt on the validity of this measurement. At this time she was doing excellent school work and her intelligence quotient was 95. Repeated examinations of the urine showed no abnormalities. A Kline test

on the blood and a spinal fluid Wassermann were negative. An electroencephalogram at the age of nine (March, 1940) showed waves strongly suggestive of grand mal epilepsy. A subsequent tracing at the age of ten (January, 1941) showed similar waves plus some dart and dome seizure patterns like those seen in petit mal.

The enuresis subsided after evening fluids were withheld but her "spells" persisted unchanged throughout the period from March, 1940 to October, 1945 despite courses of phenobarbital, benzedrine, dilantin, sodium bromide, ephedrine sulfate, glutamic acid and caffeine citrate given alone and in various combinations. Repeated urine examinations during this period showed no albuminuria or abnormal sediment.

At the age of fourteen years (October, 1945) the patient received tridione. On a dosage of 0.32 Gm. three times daily she continued to have six to seven seizures a day; three weeks following an increase in the dosage to 0.96 Gm. three times a day, the attacks were reduced to one to two a week and they stopped entirely one week later. She remained free from attacks with subsequent reduction in dosage to 0.64 Gm. and later to 0.32 Gm. three times a day; no toxic effects from the tridione were observed.

On June 22, 1946, eight and one-half months following the onset of continuous tridione therapy, pitting edema of the face and legs spontaneously appeared with a gain in weight of 18.2 Kg. over her usual weight of 67 Kg. The blood pressure was 122/70. The urine contained large quantities of protein (3+) and chemical examination of the blood revealed low serum albumin (1.8 Gm./100 ml.) and total protein (3.9 Gm./100 ml.) and elevated serum cholesterol (876 mg./100 ml.). (Fig. 1.)

* From the New York Hospital and the Departments of Pediatrics and Medicine (Neurology), Cornell University Medical College, New York, N. Y.

The red and white blood cell counts, hemoglobin concentration and differential leukocyte count were within normal limits. Tridione was discontinued. On bed rest and low salt and fluid intake, a steady loss of weight followed. By August 1, 1946, five weeks after its appearance,

pressure was elevated to 146/84 on this occasion and there was microscopic hematuria. Tridione was discontinued on October 11, 1946. By November 6, 1946, four and one-half weeks after its appearance, the edema had again subsided and the laboratory findings were again

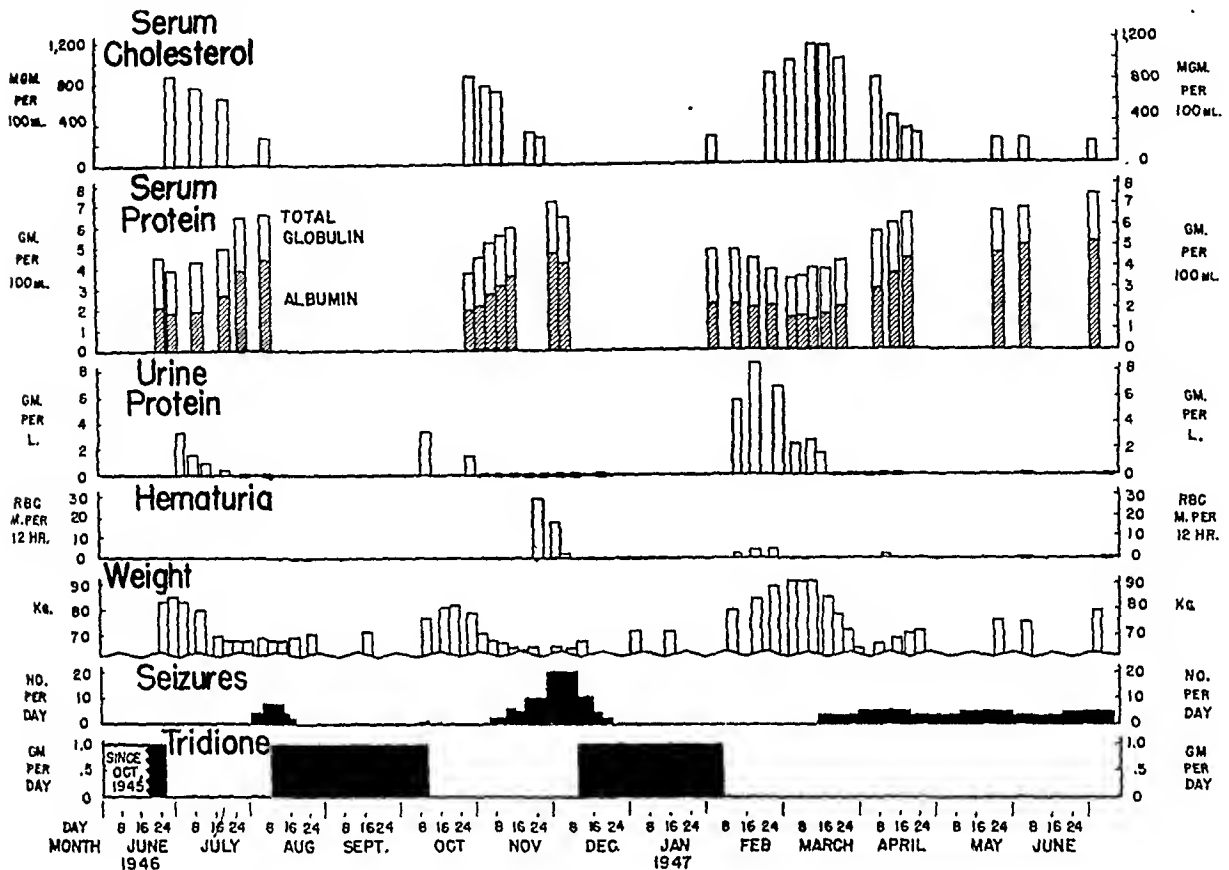


FIG. 1. Relation between occurrence of nephrotic syndrome and tridione therapy.

the edema had subsided and the laboratory findings had returned to within the normal range. At the same time petit mal seizures recurred. Because no other therapy had previously controlled the seizures and because there were no signs of persistent impairment of kidney function, 0.32 Gm. of tridione given three times a day was again started on August 9, 1946, following several test doses without detectable reaction. The frequency of seizures decreased and they stopped entirely ten days later (August 19, 1946). She returned to school.

Following this episode, the patient was free from seizures and her weight remained constant until October 4, 1946; two months after starting tridione the second time, generalized edema was again noted. Physical examination and hematologic and urinary findings paralleled those in the first episode (Fig. 1) except that the blood

normal. The seizures, however, recurred and increased in frequency as high as ten to twenty a day. Kidney function tests revealed no decrease in measurable functions. (Table 1.) The increase in severity and frequency of her seizures in the presence of normal renal function prompted the reinstitution of tridione therapy on December 10, 1946, in a dosage of 0.32 Gm. three times a day. Within two weeks her attacks had ceased a third time and she again returned to school and full activity.

On February 7, 1947, two months following resumption of tridione for the third time, edema of the face returned and again tridione was discontinued. Examination again revealed generalized edema, proteinuria, low serum albumin and total protein and high serum cholesterol. (Fig. 1.) The edema was more extensive and persisted longer in this than in the two previous

episodes. In addition there was an elevation of the blood urea nitrogen. (Table 1.) Petit mal seizures appeared on March 14, 1947, five weeks after cessation of tridione, and in this instance antedated subsidence of the edema and proteinuria. The latter cleared on March 25, 1947, five

in this clinical syndrome? Some light may be thrown on this question by an analysis of the symptoms and findings.
Description of Nephrotic Syndrome. The outstanding symptom on the three occasions was generalized pitting edema. The edema

TABLE 1*
KIDNEY FUNCTION OF PATIENT EXHIBITING NEPHROTIC SYNDROME DURING TRIDIONE THERAPY

Date	Estimated Glomerular Filtration Rate, Mannitol Clearance (C_M) ml./min./1.73 M ²	Effective Renal Plasma Flow Para-Amino Hippurate Clearance (C_{PAH}) ml./min./1.73 M ²	Filtration Fraction C_M/C_{PAH}	Effective Renal Blood Flow C_{PAH} 100-Hematocrit $\times 100$ ml./min./1.73 M ²	Maximal Tubular Excretory Capacity PAH mg./min./1.73 M ²	Urea Clearance ml./min./1.73 M ²	Blood Urea Nitrogen	
							Date	Mg./100 ml.
11-22-46	96 2	490 2	0 197	824.4	93.4	65.2	7-6-46	17.0
	(86 3-101 9) [†]	(439.3-538.4) [†]	(0 189-0 203) [†]	(749 6-900 0) [†]	(93.1-93.6) [†]	(61.5-68.9) [†]	7-11-46	14.0
11-26-46	102 2 (91 5-115 3) [†]	542.9 (486.9-595.4) [†]	0.188 (0.174-0.198) [†]	896.6 (798.1-964.7) [†]			7-23-46	16.0
							8-9-46	14.0
							10-29-46	9.0
							11-9-46	11.0
							11-12-46	9.5
							11-22-46	7.8
							12-30-46	13.0
							2-14-47	24.4
							2-20-47	31.5
							3-6-47	46.9
3-24-47	85 2	584 7	0.156	941.6	109.2	51.1	3-12-47	15.2
	(77 3-96 4) [†]	(504.2-655 5) [†]	(0 147-0.161) [†]	(818 3-1052.5) [†]	(107.3-111.1) [†]	(51.0-51.1) [†]	3-24-47	8.6
4-21-47	100.6 (85 9-108 4) [†]	567.0 (541 4-607.4) [†]	0.191 (0.178-0 198) [†]	922.0 (880.2-987.7) [†]	95.6 (88.9-107.2) [†]	65.7 (63.8-68.6) [†]	4-15-47	14.0
							4-21-47	7.8

* The clearances were performed according to the general technique described by Goldring and Chasis, Hypertension and Hypertensive Disease. P. 195. New York, The Commonwealth Fund. 1944.
† (Range of values) Number of periods.

and one-half weeks following the third episode of edema.

Repeated electroencephalograms showed consistent pathologic records strongly suggesting a convulsive disorder. Repeated electrocardiograms were interpreted as normal.

At the time of writing (September 1, 1947), the patient on phenobarbital therapy is having three to five seizures a day but she has completed her school year and has engaged in normal activity. Nephrotic symptoms and signs have been absent for five months.

COMMENT

Manifestations of the nephrotic syndrome appeared in this patient during the administration of tridione and disappeared upon withdrawal of the medication on three distinct occasions. Was tridione implicated

was accompanied by proteinuria, hypoproteinemia primarily ascribable to hypoalbuminemia and hypercholesterolemia. In each of the three remissions the proteinuria cleared, the total serum proteins and serum albumin returned to normal limits and the serum cholesterol decreased to normal levels. The results obtained in kidney function tests in two of the remissions (November 22 and 26, 1946 and April 21, 1947) and in one exacerbation (March 24, 1947) and the levels of blood urea nitrogen are shown in Table 1.

Although generalized edema was the outstanding clinical symptom and proteinuria and hypo-albuminemia were the prominent laboratory findings, the hematuria shown in Figure 1 denotes a definite

nephritis. Kidney function tests performed during the periods of remission are considered to be within the normal range. The somewhat abnormal values for mannitol and urea clearances obtained on March 24, 1947 during a period of edema may represent decreased function, especially since during this period the blood urea nitrogen was also elevated and repetition of the clearance tests performed one month later yielded normal values.

The evidence suggests that the disease which occurred during tridione therapy was the nephrotic type of nephritis not associated with persistent impairment of kidney function.

Relation of Tridione Therapy to Nephrotic Syndrome. As shown in Figure 1 the concomitant occurrence of symptoms and tridione therapy is striking. Administration of tridione, of course, could have been coincidental with a spontaneously occurring nephrotic type of nephritis or the medication could have acted only as the agent which precipitated exacerbations of an independent disease. Certainly, numerous factors such as infections, paracenteses and dietary changes among others sometimes alter suddenly, irregularly and inexplicably the course of nephrosis or mixed nephritis in children. Two facts in the present instance are against this interpretation. The regularity of the appearance of symptoms during medication and their subsidence on withholding the drug on three separate occasions certainly contrast with the irregularity of the relationship between the above mentioned factors and the spontaneously occurring disease. Moreover, complete disappearance of albumin from the urine and return of the serum proteins and cholesterol to normal levels on three distinct occasions is certainly not common during remissions of the "natural" disease.

That tridione was causally related to the nephrotic syndrome is suggested by the aforementioned variations from the spontaneously occurring disease and by the striking sequential relation between occur-

rence of symptoms and therapy. The total picture presented by this patient not only differs from the "natural" disease but is quite unlike that commonly seen with heavy metal poisoning or the toxic nephroses following use of such organic compounds as carbon tetrachloride. The quintad of intense proteinuria associated with hypoproteinemia and generalized edema, of practically normal kidney function and particularly of hypercholesterolemia is relatively rare. This combination of findings associated with drugs is not completely unknown however. So-called "gold nephrosis" has been reported⁴⁻⁸ in which edema, proteinuria, hypoproteinemia and hypercholesterolemia have been ascribed to the therapy but the same uncertainty concerning pathogenetic relationships existed in these patients. If such compounds as gold salts or tridione are shown to cause the nephrotic syndrome in some patients, an experimental approach to an understanding of the fundamental nature of the syndrome may be provided.

Final evaluation of the relation of tridione to the nephrotic syndrome must await further observations in this and other patients. Similar occurrences in other patients during tridione administration would support a causal relation. In this patient the precipitation of another attack by the administration of tridione after a prolonged remission without the drug would strengthen this thesis. Conversely, a spontaneous exacerbation in the absence of tridione therapy would be evidence for the spontaneous nature of the disease. The absence of recurrences during a prolonged period without tridione would of itself be of no significance since it might occur in either case.

The uncertainty of the rôle of tridione in the causation of a nephrotic type of nephritis in this patient has been emphasized because of the possibility of unfairly incriminating a useful drug. On the other hand, it seems worth while to record the occurrence of the nephrotic syndrome during tridione administration because it is important to call attention to all the

possible toxic effects of a new and widely used medication.

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Primary Systemic Amyloidosis with Nephrosis*

STUART LINDSAY, M.D.

San Francisco, California

PRIMARY systemic amyloidosis is a rare disease with protean manifestations. It is not often recognized during life, probably because it is not generally known that amyloidosis may occur without preceding suppuration.

In general, the sites of amyloid deposition in the primary type of disease are the heart, lungs, skin, striated muscles, mucous membranes and other tissues not usually involved in the more common secondary amyloidosis, although overlapping of the characteristics of the four types (primary, secondary, localized and that associated with multiple myeloma) has often been encountered. Forty-eight cases of primary systemic amyloidosis have been recorded in the literature,^{1,2,3,13,14} these have been summarized and the majority tabulated elsewhere.

The present report concerns an additional fatal case of primary systemic amyloidosis in which a nephrotic syndrome was the outstanding clinical feature.

CASE REPORT

S. C., No. U 12,189, a sixty-six year old white widow, was first seen on October 16, 1945. For the previous two years she had been fatigued, felt dizzy and noted increasingly severe constipation associated with rectal bleeding. During this period she had been taking 0.1 Gm. of digitalis daily without significant improvement. Eight months before entry she had had severe pharyngitis with malaise and fever lasting one week. Four months before anorexia and edema of the ankles were noted and during the next four months the level of the edema progressed to

the lower thighs. Three months before entry an examination by her physician showed; blood pressure, 104/64 mm. of Hg; urine, specific gravity 1.012, albumin 4 plus, few casts and no red blood cells. There had been no other cardiac or renal symptoms or signs.

The past and family history contained no significant items. Her last menstrual period occurred at the age of fifty-two. There was no subsequent bleeding or vaginal discharge.

The patient was an obese, elderly white woman who was lying flat in bed without apparent distress. She was cooperative but had a poor memory. Her temperature was 36.8°C., pulse 90 per minute, respiration 18 per minute and blood pressure 120/78 mm. of Hg. There was no cyanosis. Slight periorbital edema was noted. The pupils were equal and regular and reacted normally to light and accommodation. The extra-ocular movements were normal. The retinal arteries were moderately sclerotic. Both tympanic membranes were thickened. The nose, mouth and pharynx were normal. The thyroid gland was moderately and symmetrically enlarged. There was an increase in the anteroposterior diameter of the chest. The breasts were senile, atrophic and pendulous. The breath sounds over both lungs were diminished in intensity and bilateral basal râles were heard. The heart was enlarged. The PMI was felt in the fifth left interspace 2 cm. lateral to the mid-clavicular line. No murmurs were heard. The cardiac sounds were distant but had a good quality. A₂ equaled P₂. The rhythm was regular. The abdomen was obese. There was no shifting dullness. The liver edge could be palpated 6 cm. below the right costal margin. There was slight tenderness over both costovertebral angles. Mild sacral edema was noted. Examination of

* From the Division of Pathology, University of California Medical School, San Francisco, Calif.

the pelvis, rectum and nervous system revealed nothing abnormal. Except for the edema of the legs the extremities were normal.

Examination of the blood on October 16, 1945, gave the following data: Hemoglobin 118 per cent (17 Gm.); erythrocytes 5,000,000 per cu. mm.; leukocytes 7,400 per cu. mm.; neutrophilic leukocytes 60 per cent (filamented 55 per cent, nonfilamented 5 per cent); lymphocytes 38 per cent and monocytes 2 per cent. The urine was clear and yellow with a specific gravity of 1.020, albumin 4 plus, no sugar, occasional granular casts, 3 to 4 white blood cells per high power field and no red blood cells present.

Chemical investigation of the blood on October 17, 1945, showed a total serum protein of 4.27 Gm. per cent; albumin 1.9 Gm. per cent; globulin 2.37 Gm. per cent; CO_2 combining power 21.6 mEq./liter; serum chlorides 110.2 mEq./liter; non-protein nitrogen 24 mg. per cent and blood urea nitrogen 12 mg. per cent.

An Addis count done on a twenty-four hour urine specimen on October 19, 1945, showed the following: Volume 1 liter; specific gravity 1.013; pH 7; protein 13.5 Gm. per liter; leukocytes 18,000,000; erythrocytes 1,000,000; casts 500,000, all hyaline. The plasma cholesterol was 384 mg. per cent. Cultures of the urine showed no growth.

The basal metabolic rate on October 23, 1945, was plus 5 per cent. The phenosulfonthalein test gave the following results: twenty minutes, 5 per cent excretion; thirty minutes, 35 per cent excretion; sixty minutes, 15 per cent excretion; ninety minutes, 10 per cent excretion; a 65 per cent total excretion.

The rose bengal hepatic function test showed 61 per cent retention of the dye in eight minutes and 42 per cent retention in fifteen minutes. Kolmer and Kline tests of the blood were negative.

An electrocardiogram showed an abnormal record of no characteristic pattern, suggesting myocardial disease. There was moderate left axis deviation and low voltage. There also were slightly depressed S-T segments in leads I and IV, diphasic T_1 and low T_4 . Roentgenograms of the chest revealed elongation and widening of

the aorta, fibrosis at the right apex and bilateral basal pleural thickening.

Her clinical course while in the hospital was afebrile. There was a weight loss of 6.4 Kg. and almost complete disappearance of the edema. She was given a diet containing 50 Gm. of protein and less than 2 Gm. of sodium chloride per day. The clinical diagnosis was chronic glomerulonephritis (nephrotic stage).

The patient entered the hospital again on November 24, 1945. With unrestricted activity at home her legs again became edematous, in spite of a salt-free diet. Constipation and rectal discomfort continued. On November 17, 1945, she awakened with a mild chill, slight dyspnea, a temperature of 39.5°C . and a gradual onset of severe pain in the anterior right thorax. The symptoms were accompanied shortly by a mild, dry, non-productive cough. After two and one-half days of sulfanilamide therapy the fever subsided, but the orthopnea, dyspnea and cough persisted.

The physical examination revealed that the patient was apprehensive, slightly cyanotic, very orthopneic but alert and cooperative. Her temperature was 37.8°C ., pulse 100 per minute, respirations 30 per minute and blood pressure 115/70 mm. of Hg. There was moderate pitting edema of both ankles. The periorbital edema was still present. There was slight redness of the posterior pharynx. The trachea was deviated to the right. There was symmetrical enlargement of the thyroid gland. Expansion of the chest was limited. There were physical signs of bilateral pleural effusion, from the sixth interspace downward on the right and the eighth interspace downward on the left. Generalized rhonchi and moist râles were heard in the upper pulmonary fields, both anteriorly and posteriorly. The point of maximum cardiac impulse was not palpable. The heart was enlarged 4 cm. to the left of the midclavicular line in the fifth interspace; the position of the right border could not be ascertained. There was a split M_1 . A_2 equaled P_2 . The cardiac sounds were distant and of poor quality. There were no murmurs. There was mild pitting edema of the abdominal walls. The edge of the liver extended 5 cm. below the right costal margin and was not tender. Examination of the remainder of the

abdomen, back, rectum and genitalia showed nothing abnormal. The legs were grossly edematous.

Examination of the blood gave the following data: Hemoglobin 106 per cent (15.5 Gm.); leukocytes 10,600 per cu. mm.; neutrophilic leukocytes 76 per cent (filamented 61 per cent, non-filamented 15 per cent); eosinophilic leukocytes 2 per cent; lymphocytes 14 per cent; monocytes 8 per cent; uncorrected sedimentation rate 9 mm.; packed cell volume 50 and corrected sedimentation rate 16 mm. The urine was orange and turbid, pH 7.5, specific gravity 1.027, albumin 4 plus, sugar-green reduction, 5 hyaline casts, 2 granular casts, 8 waxy casts and 1 broad cast per slide; 120 leukocytes per high power field with no red blood cells present. Many additional urine specimens examined during the next six weeks gave similar findings. The feces contained 1 plus occult blood. The venous pressure was 8.2 cm. of saline. The arm to tongue circulation time (decholin) was 14 seconds.

Roentgenograms of the chest on November 25, 1945, showed moderate, bilateral pleural effusion extending to the third interspaces anteriorly. The visible portions of the lungs were clear except for the previously noted fibrosis at the right apex. There was slight displacement of the mediastinum to the right. Cultures of the blood showed only contaminating diphtheroids in forty-eight hours.

Right thoracentesis yielded dark, sanguineous fluid with a specific gravity of 1.010, 3,000 red blood cells per cu. mm., 2,300 leukocytes per cu. mm, lymphocytes 37 per cent and neutrophilic leukocytes 67 per cent. Culture of the fluid showed no growth and no acid-fast organisms could be demonstrated by guinea pig inoculation.

Chemical examination of the blood on November 26, 1945, showed the following: Non-protein nitrogen 35 mg. per cent; total serum protein 5.0 Gm. per cent; albumin 2.1 Gm. per cent; globulin 2.9 Gm. per cent; CO₂ combining power 25.1 mEq./liter; serum chlorides, 98.4 mEq./liter. On December 3, 1945, the non-protein nitrogen level of the blood was 35 mg. per cent, the CO₂ combining power, 24.7 mEq./liter and the serum chlorides, 105.6

mEq./liter. Cultures of the sputum showed the predominant organisms to be *Streptococcus viridans* and non-hemolytic *Staphylococcus albus*.

On November 28, 1945, examination of the blood gave the following data: Hemoglobin 100 per cent (14.5 Gm.); leukocytes 16,400 per cu. mm.; neutrophilic leukocytes 82 per cent (filamented 54 per cent, non-filamented 28 per cent); lymphocytes 10 per cent and monocytes 8 per cent.

No acid-fast organisms were demonstrated in the sputum by repeated smears and guinea pig inoculation. Cultures of the blood showed no growth. There were no pneumococci in the sputum.

An electrocardiogram on November 30, 1945, showed the following: Rate 125; sinus tachycardia; P-R 0.18 sec.; low voltage QRS complex; slight left axis deviation; flat T waves in all leads and low R₄.

On December 10, 1945, examination of the blood showed the following: Hemoglobin 84 per cent (12.3 Gm.); erythrocytes, 3.7 million per cu. mm.; leukocytes 9,200 per cu. mm.; neutrophilic leukocytes 82 per cent (filamented 56 per cent, non-filamented 26 per cent); lymphocytes 15 per cent and monocytes 3 per cent.

An additional roentgenogram of the chest on January 4, 1946, showed less extensive pleural effusion than previously. There was a 2 cm. rounded density superimposed upon the shadow of the right fifth rib anteriorly. There was bilateral basal pleural thickening.

From November 24, 1945 until December 11, 1945, the patient's temperature ranged between 38° and 39°C., and from December 11th to December 17, 1945, it was normal. For the next six days it remained elevated between 37.5° and 38°C. and was normal thereafter until the time of death. It was felt that there was a bilateral pneumonitis underlying the bilateral pleural effusion. A salt-free diet, which contained 80 Gm. of protein, was fed to her. Oxygen was administered continuously through a B.L.B. mask at the rate of 8 liters per minute. Fifty thousand units of penicillin were given intramuscularly every four hours and 200,000 units were administered intravenously on several occasions. Large quantities of plasma, ordinarily

500 cc. per day, were given between November 29th and December 17, 1945. This was given primarily to combat the lowered blood pressure which rarely was above 85 mm. of Hg systolic. Several transfusions of whole blood were administered during this period. Mercurial diuretics and digitalis were given intermittently.

Because no response to this regimen was apparent by December 18, 1945, and because the patient's status seemed hopeless, all therapy was discontinued and only morphine for discomfort and ammonium chloride to produce diuresis were given. During the next three weeks there was an apparent complete clearing of the pneumonic process. The blood pressure remained below 90 mm. Hg systolic. Throughout the illness the patient was anorexic and her intake of protein was far below the prescribed amount.

On January 12, 1946, the patient climbed over the side rail of the bed and fell to the floor. There was no evidence of injury but later during the day her temperature suddenly became elevated to 38°C., coarse tracheal rhonchi appeared the pulse rate rose to 144, the patient became extremely dyspneic and cyanotic and expired within a few hours.

The autopsy (UA.46:6) was performed four and one-half hours after death. The body was extremely obese and there was massive edema of the subcutaneous tissues, especially in the lower extremities. The head, eyes, ears, nose and mouth were not grossly altered. One to 2 mm., slightly elevated, brown, macular and reddish angiomatous lesions were present on both forearms. The peritoneal cavity was normal and did not contain an excessive amount of fluid. The liver edge lay between 2 and 4 cm. below the costal margins and the xiphoid process.

The right pleural cavity contained approximately 3,000 cc. of clear yellow fluid and clotted fibrin. About 1,000 cc. of similar material were present in the left pleural cavity. There were both fibrous and fibrinous pleural adhesions at the apices and the bases. No thymic glandular tissue was evident. The pericardial cavity contained 100 cc. of clear fluid and there was no alteration of the pericardial surfaces.

The heart weighed 360 Gm. It had a smooth, glistening visceral pericardium which contained a normal amount of fat. The ventricular myo-

cardium, especially on the left side, was firm and had a pale yellowish-tan color. Throughout the left ventricular wall, especially near the apex, narrow, fine, grayish, translucent streaks were visible between the muscular bundles. This material stained a deep mahogany brown with a strong solution of iodine, U.S.P. The left ventricle averaged 1.5 cm. in thickness and the right ventricle 0.5 cm. in thickness. The left auricular wall was thickened, measured 3 mm. in thickness and had a leathery consistency. The right auricular wall averaged only 1 mm. in thickness and was of normal consistency. The left ventricular endocardium was normal. The endocardium of both auricles was studded with tiny, 0.5 mm., slightly elevated, rounded, translucent, grayish nodules. Several 2 mm., pale, yellow, fibrous nodules were noted in the endocardium of the right ventricle. The aortic and mitral valves contained small, yellow, atheromatous plaques. Approximately 0.5 cm. from the free edge of the left leaflet of the tricuspid valve was a subendothelial, translucent, ovoid nodule measuring 0.5 cm. in diameter. The valves measured as follows: AV 7.5 cm., MV 10 cm., PV 8 cm. and TV 12.5 cm. There was no gross alteration of the coronary arteries; the coronary ostia were patent. Moderate dilatation of the right side of the heart, especially of the right auricle, was present. A large, firmly adherent, dry, friable, antemortem thrombus was found in the right auricular appendage.

The right lung weighed 540 Gm. and the left lung 480 Gm. The mucosa of the major and smaller bronchi was congested. There were scattered yellowish opaque, atheromatous plaques in the intima of the major branches of the pulmonary artery. Several of these arterial branches contained adherent, dry, firm, twisted, antemortem thrombi. Both lungs were diffusely congested and edematous. Posteriorly and inferiorly they were partially atelectatic, the result of pressure by the pleural fluid. Two wedge-shaped infarcts, measuring 3 and 5 cm. in diameter respectively, were found in the lower and lateral portions of the lower lobe of the left lung. The larger was of more recent origin and had a reddish wet surface; the smaller was pale and firm. The main pulmonary artery of the lower lobe of the left lung was completely

obstructed by an antemortem thrombus. In the lower lobe of the right lung and in the apex of the right lung similar 3 to 4 cm., triangular-shaped infarcts were demonstrated. The pleural surfaces were smooth and glistening. The hilar lymph nodes showed nothing abnormal.

The liver weighed 1,480 Gm., and was normal in size and appearance. No amyloid could be demonstrated by staining with a strong solution of iodine, U.S.P. There was mild thickening of the wall of the gallbladder and the lumen contained several faceted 1.5 cm. cholesterol stones. A similar stone was found in the cecal lumen. The extrahepatic bile ducts and pancreas were normal. The spleen weighed 120 Gm. Its capsule was smooth. The cut surface had a deep red color and a fibrous, dry consistency. The gastroenteric tract had a grossly normal appearance throughout its extent. The mesenteric and preaortic lymph nodes were small. The adrenal glands were of normal size; an occasional adenomatous nodule was noted in the cortical layers.

The right kidney weighed 240 Gm., and the left 250 Gm. The blood vessels of the renal pedicles were normal. The capsules were slightly adherent and the subcapsular surfaces were finely granular, pitted and pale yellow in color. On the cut surfaces the cortical layers appeared pale and yellow in color. They were soft, opaque and striated; the demarcation from the deep red medullas was less distinct than normal. Punctate, deep brown spots appeared throughout the cortical layers when the tissue was stained with a strong solution of iodine, U.S.P., indicating the presence of amyloid substance in the glomeruli. There was slight dilatation of the renal pelvis and a few small petechial mucosal hemorrhages were observed. The ureters and bladder were normal. The internal genitalia were atrophic but otherwise not unusual. Minimal atherosclerosis was evident in the aorta. The thyroid gland was moderately enlarged; its substance had a normal color and consistency. On the posterior capsule of the thyroid gland four parathyroid glands were found; these were enlarged approximately two to three times. The brain weighed 1,240 Gm. The meninges were grossly normal. The external blood vessels showed no thickening of their walls. Both ex-

ternally and on section the cerebral hemispheres, the cerebellum and the brain stem were entirely normal. The pituitary gland was of normal size.

Microscopically all portions of the examined myocardium were distinctly altered. There was extensive interstitial and pericellular deposition of hyaline, eosinophilic material which stained specifically for amyloid substance with the Congo red and crystal violet stains. (Fig. 1.) The pericellular amyloid formed an imprisoning sheath or ring about the individual muscle fibers. Where the rings were thicker and the interstitial amyloid most abundant the myocardial fibers were atrophied or completely absent. Other muscle cells showed degenerative changes with vacuolization and deposition of pigment granules. In most myocardial regions the fibers appeared essentially normal, even though all were surrounded by amyloid rings of varying thicknesses. Narrow amyloid deposits also surrounded the individual fat cells of the epicardial layer. The amount of subendothelial endocardial amyloid varied in different portions of the heart. It was most abundant in the right auricular wall where the material often projected into the cardiac lumen. Here it was generally covered by an endothelial layer. In the right auricle an organizing antemortem thrombus lay immediately adjacent to the large, endocardial amyloid deposits. Almost all the blood vessels of the heart, including arteries, veins and capillaries, contained small, subendothelial, rounded, irregular, amyloid deposits. None of these seriously narrowed the lumen of these vessels. All of the cardiac valves contained small, deep, interstitial, amyloid deposits; this material formed the translucent nodule seen in the tricuspid valve.

Almost all the pulmonary arteries, veins and arterioles contained amyloid deposits in their walls. The branch of the pulmonary artery leading to the lower lobe of the left lung contained large, irregular amyloid clumps, chiefly in a subendothelial situation. The lumen of this vessel was largely occluded by a well organized thrombotic mass. In other large pulmonary arteries where the amyloid was less abundant, thrombi of more recent origin without organization were noted. In the smaller vessels containing the most abundant amyloid thrombosis had also

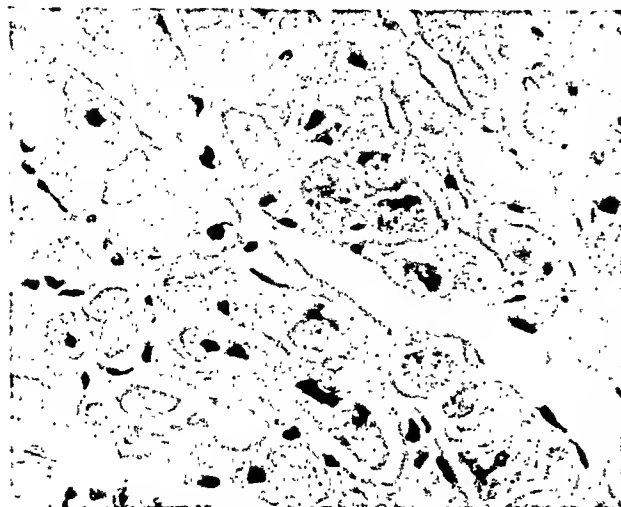


FIG. 1. Pericellular amyloid infiltration in the myocardium; hematoxylin and eosin $\times 500$.

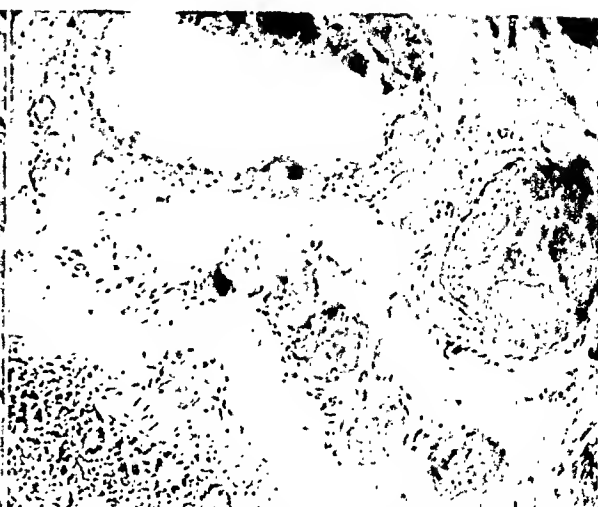


FIG. 2. Amyloid infiltration of duodenal blood vessels; hematoxylin and eosin $\times 120$.

occurred. Almost all the alveolar walls were thickened as the result of amyloid deposition about the capillaries of the alveolar walls. The pulmonary infarcts were hemorrhagic and showed varying degrees of surrounding inflammatory reaction and organization. Adjacent to the infarcts the vascular amyloid infiltration, thrombosis and vascular obstruction were greater than elsewhere. In the pulmonary parenchyma the small bronchi and bronchioles contained purulent exudate.

The hepatic parenchyma was essentially normal except for mild congestion of the central sinusoids. Subendothelial amyloid deposits were observed in almost all the small hepatic arteries. There was lymphoid atrophy of the spleen. The central arteries and arterioles were thickened and hyalinized but only a few contained amyloid material. The splenic pulp was fibrotic and the reticuloendothelial cells often contained brown pigment. Except for one small zone of interstitial fibrosis the pancreatic parenchyma was normal. A small number of the arterioles contained subendothelial amyloid deposits. Similar vascular deposits were present in the wall of the gallbladder.

All portions of the gastroenteric tract showed a similar histologic alteration. There were extensive amyloid deposits in the walls of the mucosal and submucosal blood vessels, including arteries, veins and capillaries. (Fig. 2.) Pericellular amyloid deposits were observed about the individual smooth muscle cells and also

surrounding the fat cells of the subserosal layer. The most extensive muscular involvement was in the muscularis mucosa. The largest amyloid deposits were in the stomach and duodenum, with considerably less in other portions of the gastroenteric tract. The cellular layers of the adrenal glands were not significantly altered, although there were small masses of amyloid material in the walls of the smaller capsular vessels and about the fat cells in the periadrenal tissues.

With few exceptions the renal glomeruli contained pericapillary amyloid deposits. (Fig. 3.) Almost all the glomerular capillaries were narrowed but only a few glomeruli had been completely replaced by amyloid substance. The endothelial and epithelial cells of the damaged glomeruli were compressed and atrophic; there was no cellular proliferation. In most of the glomeruli, Bowman's capsule was thin and normal; in a few, the capsule showed a fibrous or amyloid thickening. Some afferent arterioles contained subendothelial amyloid deposits while some were occluded by this process. The tubules were severely damaged, especially those of the convoluted group. Many were dilated and nearly all contained hyaline casts. There was considerable cellular swelling; lipid droplets were often encountered in the degenerating cells. Capillary amyloid infiltration outside of the glomeruli was not demonstrated but there were many small interstitial amyloid deposits in the cortical layers. Small accumulations of

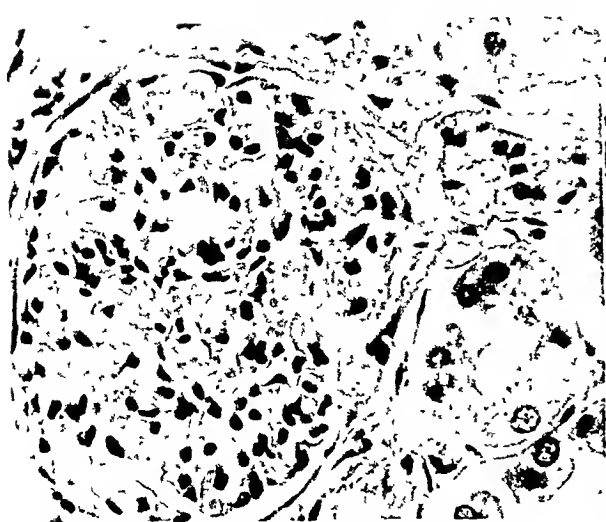


FIG. 3. Glomerular amyloid infiltration; hematoxylin and eosin $\times 500$.

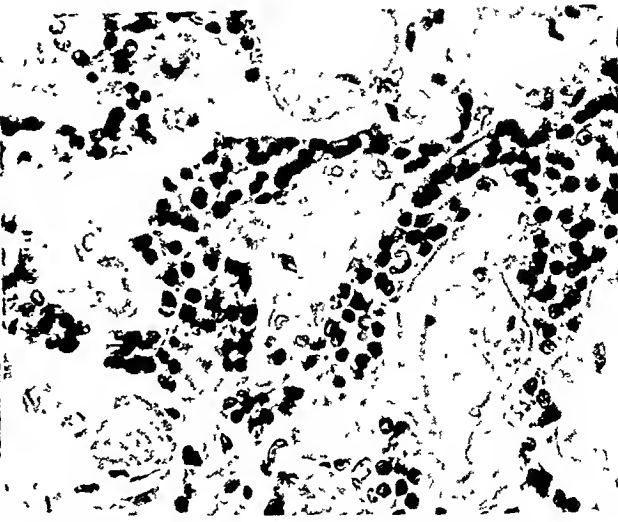


FIG. 4. Parathyroid amyloid infiltration; hematoxylin and eosin $\times 500$.

interstitial lymphocytes and zones of scarring were scattered throughout the cortical layers and were most numerous in areas where the amyloid infiltration was greatest. The small vessels in the medulla and pelvic tissues contained subendothelial amyloid deposits. The arcuate arteries showed only minimal amyloid infiltration. The pelvic submucosa was edematous and showed small hemorrhages and lymphocytic collections.

The layers of the bladder were normal but almost all the arterioles contained amyloid masses. The internal genitalia were atrophic but not otherwise unusual. Only a few of the small ovarian and tubal blood vessels contained amyloid deposits. There was atrophy of the breast parenchyma. Small amounts of capillary amyloid were present in the pituitary gland. The thyroid acini were slightly reduced in size, were lined by tall cuboidal epithelium and were filled with evenly staining colloid which was vacuolated at the margins. There was amyloid infiltration of the walls of the small thyroid arteries and about the fat cells near the capsule. Even though the parathyroid glands were enlarged there was no cellular hyperplasia. The increase in size was the result of extensive amyloid deposition in the interstitial connective tissues surrounding the individual stromal fat cells. (Fig. 4.) Compression and destruction of some of the glandular tissue had occurred. A few small, typical atheromatous plaques were noted in the aortic intima. The media was not altered. There were a few small vessels in the adventitial layer

which were infiltrated with amyloid material. All the lymph nodes had a normal histologic appearance and contained no amyloid. There were only a few small interstitial masses of amyloid substance present in the dermal layer of the skin. The bone marrow showed a normal cellular distribution; amyloid material and plasma cells were absent. The central nervous system had an entirely normal microscopic appearance and contained no demonstrable amyloid material.

COMMENTS

In secondary amyloidosis the kidney is a common site of amyloid deposition. The variability of the manifestations of renal amyloidosis depends upon the amount and extent of the amyloid infiltration.⁴ Minimal amounts of glomerular amyloid produce insufficient injury to cause albuminuria. With larger amounts of glomerular amyloid there is a more severe glomerular injury which is then associated with albuminuria. This may lead to hypoproteinemia, lowering of the osmotic pressure of the plasma and generalized edema. With still greater glomerular, vascular and interstitial amyloid deposition, renal insufficiency, at times associated with hypertension, follows. It is apparent that amyloid nephrosis is a type of moderately advanced renal amyloidosis

and that the lipid degenerative changes in the tubules are the result of diminution of glomerular blood flow.⁵

Of the forty-eight recorded cases of primary systemic amyloidosis twenty-five had some degree of renal amyloidosis. In the majority of these there was minimal glomerular or vascular amyloid infiltration, associated in a few instances with albuminuria as the only manifestation. In three patients there was a progressive, fatal azotemia.^{6,7,8} In Gerber's case⁹ a nephrotic syndrome, associated with hypercholesterolemia, normal renal function, albuminuria, a positive Congo red test and normal blood pressure, persisted for over two years and was followed by renal insufficiency and hypertension, the result of increasing amyloid infiltration of the kidneys. In an additional case recorded by Christian,¹⁰ and later by Dillon and Evans,¹¹ a typical nephrotic syndrome¹² was the outstanding manifestation of amyloidosis of the primary type.

SUMMARY

A fatal case of primary systemic amyloidosis is reported. The patient was a sixty-six year old woman who presented the clinical and laboratory signs of nephrosis.

Widespread amyloid infiltration was demonstrated at autopsy and renal amyloidosis accounted for the nephrotic syndrome.

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American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE MIDWESTERN SECTIONAL MEETING

HELD IN CHICAGO, OCTOBER 30, 1947

**GLUTAMIC ACID AND VOMITING IN DOGS:
A COMPARISON OF ITS ADMINISTRATION
INTO THE PORTAL SYSTEM AND EXTREMITY
VEINS.** *A. G. Lasichak, M.D. and S.
Levy, Ph.D. (by invitation), Eloise, Michi-
gan.* (From the Wayne County General
Hospital.)

It has been shown that the intravenous administration of glutamic acid may produce nausea and vomiting in both man and animals. However, large amounts of glutamic acid may be taken orally without producing these reactions. This difference may be due to the rôle of the liver in detoxifying the orally administered glutamic acid. In this study two routes were used for infusion into the portal system: the intrasplenic route and direct injection into the portal vein. The first method was achieved by transplanting the spleen subcutaneously in five dogs and administering the solution of glutamic acid directly into the spleen by means of a needle. Direct infusion into the portal vein was accomplished by using a modified London angiostomy technic in two dogs. All animals received an infusion of 1.4 Gm. of glutamic acid and 0.4 Gm. of sodium bicarbonate per 100 ml. The solution was injected at a constant rate until vomiting occurred, and the volume necessary to produce vomiting was used as an index of tolerance. In all of the twenty-six tests carried out the amount of glutamic acid infused intraportally exceeded the amount given intravenously for any given animal. The blood amino acid nitrogen and urea plus ammonia nitrogen were determined. No striking differences were found. The results indicate that intraportal administration of glutamic acid is better tolerated than the intravenous route

because of detoxification by passage through the liver.

**RENAL FUNCTION IN GENERAL ANESTHESIA:
A CLINICAL STUDY OF CHLOROFORM.**
E. B. Cohen, M.D., Madison, Wisconsin.
(From the Departments of Medicine and
Anesthesiology, University of Wisconsin
Medical School.)

Eighty patients subjected to major surgical procedures were studied before and after operation. In forty instances the anesthetic agent was chloroform, and in forty cases a general anesthetic agent other than chloroform was used. These control cases were: ether, twenty; cyclopropane, seven; tribromethanol, seven; vinethene, six. Anesthesia was of long duration averaging two hours for both the chloroform and the control groups. The operations performed were all extensive. There were no important differences in sex incidence or age distribution.

Over 200 urea clearance and PSP excretion tests and a larger number of NPN determinations and urinalyses were done in the early postoperative period. No significant differences in renal function between the forty chloroform and forty control cases were observed. Similarly, serial postoperative blood sugar and alkali reserve determinations showed no notable differences between the chloroform and control groups.

It is suggested that the postoperative derangements of homeostasis and renal function often attributed to the toxic effects of anesthetic drugs on the kidney are actually extrarenal in origin. The uniformity of apparent depression of renal function which we have observed regardless of the agent used would support this conclusion.

TRANSPORT AND EXCRETION OF URIC ACID IN MAN. III. PHYSIOLOGIC SIGNIFICANCE OF THE URICOSURIC EFFECT OF CARONAMIDE. *W. Q. Wolfson, M.D., C. Cohn, M.D., R. Levine, M.D. and B. Huddleston, M.D. (by invitation), Chicago, Illinois.* (From the Departments of Biochemistry and Metabolic and Endocrine Research, Medical Research Institute, Michael Reese Hospital.)

In normal adults following oral administration of a single 4.6 Gm. dose of caronamide the true urate excretion increases from 50 to 120 per cent within two hours. Simultaneously the plasma urate falls slightly and the urate clearance increases to about twice its original value. The glomerular filtration rate remains at about the fasting value.

This effect is similar to that produced by other drugs (cinchophen, salicylate, diodrast, salyrgan) all of which produce a simultaneous increase in minute excretion of urate and a decrease in plasma urate concentration. This pattern of pharmacologic actions has been termed the "uricosuric effect."

Most previous workers believed the uricosuric effect to be due to inhibition of tubular reabsorption of urate but a number of considerations indicate that this is improbable. Both caronamide and benzoate block the tubular excretion of penicillin; yet caronamide has a uricosuric effect while benzoate has precisely the opposite effect upon urate excretion. Both sorbitol and mannitol are cleared at the glomerular filtration rate; but sorbitol gives a striking uricosuric effect while its stereoisomer, mannitol, does not. Certain other substances which produce the uricosuric effect are effective in such small amounts that it is difficult to believe their action to be due to direct blocking of a tubular reabsorptive mechanism. A list of more than forty uricosuric agents which we have compiled includes substances excreted by filtration and reabsorption, by filtration and tubular excretion, and by filtration alone. Such diversity of excretory mechanisms makes it improbable that all share the ability to block the reabsorption of urate by the tubules.

Elsewhere we have presented data which indicate that there is normally little or no tubular reabsorption of urate. All of the urate passing the glomerulus appears to be excreted in the urine, with the possible exception of a

small fraction undergoing back-diffusion. This appears to depend upon the fact that only a small proportion of the plasma urate is freely diffusible through the human glomerulus. The action of caronamide, and possibly that of the other uricosuric drugs, may be understood by postulating that such agents increase the fraction of the plasma urate which passes the glomerular filter.

OCCURRENCE OF GASTRIC NEOPLASMS IN YOUTH. *M. Block, M.D., A. H. Grieb, M.D. (by invitation) and H. M. Pollard, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan.)

The primary obstacle to making a diagnosis of carcinoma of the stomach in youth appears to be the patient's age. Since only limited information is available, it was believed that the usual clinical dictum that a gastric lesion in a patient below the age of thirty-one is probably benign was not necessarily justified.

In a study of this problem the following information was obtained: (1) A survey of the occurrence of carcinoma of the stomach during a twenty-year period (1925 to 1945) at the University Hospital revealed that there were 1,913 carcinomas in a total of 453,400 registrations. This is an incidence of 0.42 per cent. (2) Of the 1,913 carcinomas during this period, twenty cases occurred in patients below the age of thirty-one (an incidence of 1.04 per cent of all gastric carcinomas seen). Seventeen of these twenty cases had metastases when first examined, and the diagnosis of carcinoma was usually delayed because benign gastric ulcer was generally considered in view of the patient's youth. (3) During the same twenty-year period, fifty-three other gastric lesions occurred in the same age group (fifty benign gastric ulcers, two gastric lymphoblastomas and one gastric lues). (4) These figures demonstrate that all gastric lesions are rare in patients below the age of thirty-one, but when a gastric lesion does occur, the probability of its being neoplastic is at least 30 per cent.

HEMOCHROMATOSIS WITH APLASTIC ANEMIA.

F. R. Schemm, M.D., E. Hildebrand, M.D. (by invitation), F. H. Crago, M.D. (by invitation) and J. A. Layne, M.D., Great Falls, Montana. (From the Departments of Medicine and Pathology, Great Falls Clinic.)

Severe anemia is an uncommon finding in hemochromatosis. However, several cases of aplastic anemia accompanying hemochromatosis have been reported. We have observed a fifty year old man whose principal complaint was weakness. Physical examination was essentially normal. Examination of the blood revealed a slight anemia and leukopenia, a prolonged bleeding time and a complete lack of clot retraction at forty-eight hours. The bone marrow was found to be active and the proportion of cells normal. There was no hematologic response to iron or liver therapy. The erythrocyte and leukocyte counts gradually declined. A diagnosis of primary splenic neutropenia was entertained and splenectomy was performed. A histopathologic diagnosis of hemochromatosis was made. The patient failed to respond clinically and the hemotologic findings remained unchanged. Repeated blood transfusions were necessary to maintain life. Glycosuria was never demonstrated but the glucose tolerance curve was elevated. About four years after onset of symptoms the patient died. Necropsy revealed iron pigment in most of the parenchymatous organs except the pancreas.

This man was continuously employed for many years in a copper refinery. Mallory and others have drawn attention to the association of hemochromatosis with exposure to copper. This case supports this concept.

QUANTITATIVE ESTIMATION OF STERNAL BONE MARROW ACTIVITY IN PERNICIOUS ANEMIA. *A. S. Weisberger, M.D. (by invitation) and R. W. Heinle, M.D., Cleveland, Ohio.* (From the Department of Medicine, School of Medicine, Western Reserve University.)

Estimation of the activity of the sternal marrow based upon the values of the nucleated cell count, myeloid-erythroid volume and fat content obtained from 1.0 ml. of aspirated material is frequently unreliable. When these values are compared with the actual histologic appearance of the marrow, wide discrepancies are sometimes encountered. This is especially true in cases in which the bone marrow is composed of densely packed cohesive cells, as in pernicious anemia in relapse.

In this study the histologic appearance of the sternal marrow was compared with the values for the nucleated cell count and volumetric

pattern obtained from 1.0 ml. of aspirated material in cases of pernicious anemia. Histologic sections of marrow particles, the nucleated cell count and the volumetric pattern were all obtained from the same sample.

In most patients with pernicious anemia in relapse, low values were obtained for the nucleated cell count and myeloid-erythroid volume, indicating normal or decreased activity. However, the histologic sections revealed densely packed, markedly hyperactive marrow. In the cases of treated pernicious anemia the values for the nucleated cell count and myeloid-erythroid volume were within normal limits and the histologic sections showed normal cellular activity.

The lack of correlation between the nucleated cell count, myeloid-erythroid volume and histologic appearance in cases of pernicious anemia in relapse is thought to be due to the density and cohesiveness of the marrow which resists separation on aspiration.

ABSORPTION AND EXCRETION OF CHORIONIC GONADOTROPHIN. *W. E. Brown, M.D. and J. T. Bradbury, Sc.D. (by invitation), Iowa City, Iowa.* (From the Department of Obstetrics and Gynecology, University of Iowa.)

Human chorionic gonadotrophin has been shown to have a luteotrophic function in the woman. In appropriate dosage it will induce a pseudopregnancy as demonstrated by a delay in menses, persistence of pregnandiol excretion, prolongation of the life of the corpus luteum, decidual changes in the endometrium and a positive Aschheim-Zondek reaction. Five thousand I. U. daily was shown to be a minimum effective dose when the hormone was given intramuscularly in aqueous solution.

Because of the cost and difficulty in preparing a pyrogen-free material for intramuscular use, studies were undertaken to find alternate methods for administering this hormone. Chorionic gonadotrophin was given by various routes to a series of women in doses ranging from 2,500 to 1,000,000 I.U. Urinary excretion of chorionic hormone was determined by the Aschheim-Zondek reaction in rats.

After intramuscular injection of 10,000 I. U. of gonadotrophin the hormone appeared in the urine in such quantities that it could be demonstrated in urine volumes equivalent to a three-minute output. Excretion occurred in the first

six hours after administration in aqueous solution. When injected in a wax and oil medium the rise in urinary levels was delayed about eighteen hours. Consistently positive Aschheim-Zondek tests were not obtained with three-minute urine volumes later than thirty hours after an aqueous solution was given, whereas the tests were positive forty-eight hours after the wax preparation was injected. When the hormone was given as an emulsion, the urinary excretion findings indicated only a slight delay in initial absorption and persistence through the forty-eight-hour test period.

When given orally in plain or salol-coated capsules in doses as high as 200,000 I.U., the hormone was not excreted in detectable amounts. When a Miller-Abbott tube was passed into the ileum and 300,000 I.U. of hormone was introduced, even a three-hour urine volume did not contain any trace of hormone, and increasing the dose to 1,050,000 I. U. resulted in only a trace of hormone in a three-hour urine volume. Similarly, 123,000 I. U. introduced as a retention enema was followed by the appearance of only a small amount in the urine. From these experiments it is obvious that enteral administration is not feasible due to the destruction of the hormone in the gastrointestinal tract.

EFFECT ON FETAL RESPIRATION OF METHIDON ADMINISTERED DURING LABOR. *A. C. Barnes, M.D. and (by invitation) F. B. Hapke, M.D., Columbus, Ohio. (From the Ohio State University Medical School.)*

The present study is concerned with the respiratory depressant effects on the fetus of methidon administered to the mother during labor.

Ninety patients have been delivered under low spinal or caudal anesthesia. No drugs other than the ones under study were administered systemically. The times of the first fetal respiration and of the first lusty cry were clocked for each delivery. Thirty patients served as a control group and received no systemic medications. Thirty patients received methidon at varying intervals prior to delivery. Thirty patients received demerol to serve as additional controls.

On the basis of these studies we believe that: (1) The experimental method used here offers the most valid approach to the study of neonatal narcosis available to date. (2) Regardless of time intervals prior to delivery, 10 mg. of methidon

is without significant effect on fetal respiration. (3) A 15 mg. dose of methidon, if administered three hours or less before delivery, produces a significant delay in the first respiration and first lusty cry. If the time interval is greater than three hours, little depressant effect could be noted. (4) Methidon administered under these circumstances is a more marked respiratory depressant than demerol.

EFFECT OF GERMAN MEASLES DURING PREGNANCY. *Stuart Abel, M.D. (by invitation) and T. R. Van Dellen, M.D., Chicago, Illinois.*

A request for letters from mothers who had had German measles during pregnancy was included in a syndicated health column. They were asked to state the exact month of gestation that the illness occurred and the effect on the offspring. Over ninety replies were obtained and of these, eighty-two were considered acceptable. The series includes two sets of twins, making a total of eighty-four children.

Three stillbirths were recorded from mothers having German measles during the first trimester of pregnancy. Twenty-five of the children were normal at birth. In seven of these the mother contracted the disease during the first trimester, eleven during the second and seven in the last. Fifty-six of the infants were abnormal at birth, thirty-six with a single defect and twenty with more than one defect. In forty-four (76 per cent) of these, the mother told of having German measles during the first trimester of pregnancy, eight in the second, one in the third and unknown in three. Nineteen of the infants had congenital heart disease, seventeen had cataracts, fourteen were deaf, and seven were mentally deficient. Gastrointestinal, eye, spinal and skeletal abnormalities also occurred in lesser numbers.

The most serious defects or combination of defects occur in women having German measles during the first trimester; defects are less serious and more infrequent in the second. Only one abnormal child was born in the third trimester group. The diagnosis was cerebral palsy and was not considered to be related to the mother's illness.

Statistics obtained reveal that 87 per cent of the babies born of mothers having German measles during the first trimester were abnormal. No abnormalities developed in the third trimester.

CYCLAINE (D-109), A NEW LOCAL ANESTHETIC AGENT. *R. M. Wylde, M.D. (by invitation), D. M. Waters, M.D. (by invitation) and O. S. Orth, M.D., Madison, Wisconsin.* (From the Departments of Anesthesiology and Pharmacology, University of Wisconsin.)

Cyclaine (D-109) is 1-cyclohexylamino-2-propylbenzoate hydrochloride. Preclinical tests on experimental animals have indicated both a greater anesthetic potency and toxicity but a comparable therapeutic ratio to procaine. The duration of action was equivalent to pontocaine. A preliminary clinical evaluation of cyclaine for spinal analgesia has been made on forty patients.

The site of dural puncture was at lumbar 3-4. Twenty-five to 35 mg. of the drug from a sterile 0.5 per cent solution was used in seven patients. With this preparation onset of analgesia was quite slow, requiring twenty to thirty minutes to develop completely. It then persisted for over two hours.

In thirty-three patients 20 to 50 mg. was administered in a 1 per cent solution of spinal fluid. With this alteration analgesia occurred within sixty seconds and motor paralysis within three to six minutes. Analgesia lasted two hours or longer. The blood pressure declined comparable to the response to other agents, and treatment was similar. Pulse rates also declined. There was slow localization of the level of analgesia. A progressive paralysis of the upper thoracic segments occurred in a patient placed in the Trendelenburg position fifteen minutes after administration of the drug. No serious complications were observed.

Operations which have been performed include inguinal herniorrhaphy, hemorrhoidectomy, vaginal hysterectomy, transurethral prostatic resection, excision of anal fissure, fulguration of bladder tumor, resection of carcinomas of the sigmoid and cecum, cholecystectomy, gastrostomy and appendectomy.

MUSCULAR SYMPTOMS OF ALLERGIC ORIGIN.

Theron G. Randolph, M.D., Chicago, Illinois.

Allergic muscle symptoms were described by Rowe as part of the clinical picture of "allergic toxemia," more recently reviewed by the writer as the fatigue syndrome of allergic origin. This clinical reaction is usually due to masked food allergy, a concept of food sensitization described

by Rinkel which aids in explaining the chronic, smoldering clinical reactions commonly resulting from the oft-repeated ingestion of allergenic foods. Such a mechanism accounts for the fact that patients are rarely able to detect sensitivity to the most important foods such as corn, wheat, milk and eggs because symptoms are usually improved temporarily following the ingestion of a masked food allergen, becoming worse several hours later, particularly during the night or on arising in the morning.

Generalized muscle symptoms consists of aching, lameness, stiffness and soreness. Localized reactions involve the muscles of the nuchal region, particularly the trapezius and the sternocleidomastoid, either unilaterally or bilaterally, and are commonly associated with allergic headaches. Attacks characterized by tightness, tenseness, pulling, drawing or "knotty" sensations in these muscles have been induced experimentally after the test feeding of allergenic foods. Increased tonus and tenderness of the involved muscles may often be demonstrated by palpation. Acute "wry neck" has also been observed under the same circumstances.

The heavy muscles of the lower back may react similarly, giving rise to the complaint of backache. Tightness, "knotty" sensations and localized pain have been observed less frequently in the hamstrings, gastrocnemius, intercostals and the muscles about the shoulder girdle. These muscle symptoms are improved by massage and have been observed to subside with the elimination of specific food allergens.

EFFECT OF PENICILLIN ON THE BLOOD CLOTTING MECHANISM. *R. E. Dolkart, M.D., B. Halpern, M.S., M. Larkin, B.A. and Geza de Takats, M.D., Chicago, Illinois.*

The widespread use of penicillin in a variety of clinical conditions makes any effect of penicillin on the clotting activity of blood of considerable importance. Because of the conflicting reports and the frequent occasions in which penicillin may be used in the presence of altered clotting mechanisms, further studies seemed appropriate.

Penicillin was administered to normal subjects and clotting activity studied by the heparin tolerance test and prothrombin time. The heparin tolerance curve was analyzed and classified into group and heparin reactor group response.

The group heparin tolerance curve and prothrombin time was not significantly altered by penicillin. The heparin reactor groups, hypo-, normo- and hyperreactors, showed a change of borderline statistical significance after penicillin, but still remained within the normal limits of the analyzed group heparin curve.

ADMINISTRATION OF MASSIVE DOSES OF VITAMIN P. HESPERIDIN METHYL CHALCONE. *W. R. Kirtley, M.D. and F. B. Peck, M.D., Indianapolis, Indiana.* (From the Lilly Laboratories of Clinical Research, Indianapolis General Hospital.)

The clinical effect of vitamin P substances has been controversial and information has been based largely on observations of the petechial index as determined by one of the positive or negative pressure methods. These methods at best are but crude approximations, as there are several known factors which influence the results. Little is known about the absorption, utilization and excretion of vitamin P. The bulk of animal and clinical studies supports the contention that these flavones do have a definite influence on capillary permeability as distinguished from the capillary fragility of scurvy which responds to ascorbic acid.

Hesperidin chalcone has been identified as the unstable, water-soluble, yellow pigment from crude orange hesperidin which on methylation is stabilized without affecting its vitamin P activity. Since some of the conflicting reports may be due to inadequate dosage or lack of an appropriate test method, repeated observations were made of the blood concentration before and after constriction in cases in which capillary permeability was presumably affected. Criteria of effect were the total protein, albumin and globulin, hemoglobin, erythrocyte count, hematocrit and modified Gothlin's test. Simultaneously the urinary excretion of hesperidin methyl chalcone was measured by the colorimetric borocitric method.

The findings in general indicate that the changes in concentration of blood proteins, erythrocytes, hemoglobin, hematocrit and petechial index are too variable to be statistically significant. As much as 15 Gm. daily have been administered without any evidence of toxic effect. Excretion rates were elevated above the levels of controls but did not show any quantitative relationship to the amounts administered. It is suggested that the flavone may not be

quantitatively absorbed, that it undergoes changes in the body into substances incapable of reacting in the borocitric test or that large doses may induce tachyphylaxis.

EFFECT OF INTRAVENOUS ADMINISTRATION OF NICOTINIC ACID ON BLOOD BILIRUBIN. *W. D. Gambill, M.D., B. D. Rosenak, M.D., J. E. Fisher, M.D. and R. H. Moser, M.D. (introduced by K. G. Kohlstaedt, M.D.), Indianapolis, Indiana.* (From the Gastrointestinal Clinic of the Indianapolis City Hospital.)

Marfori, Stefanini and Barmante have reported that following the intravenous injection of nicotinic acid there is a rise of blood bilirubin. They have attempted to adapt this observation to the study of the excretory function of the liver and have suggested that it may constitute an endogenous bilirubin tolerance test. The normal bilirubin curve following the injection of nicotinic acid consists of an initial rise of blood bilirubin with a gradual return to normal over an eight-hour period. We have confirmed this observation in eleven normal individuals.

Twenty-one patients with a variety of liver diseases were studied. Four distinct types of bilirubin curves were obtained. No type of curve was typical of any specific liver disease. In five cases of extrahepatic biliary obstruction no diagnostic type of curve was demonstrated. As a test of liver function it was found the bilirubin curve did not parallel other accepted liver function tests.

STUDIES ON DERMAL HYPERSENSITIVITY IN HUMAN BRUCELLOSIS. *A. I. Braude, M.D., W. H. Hall, M.D. and W. W. Spink, M.D., Minneapolis, Minnesota.* (From the Division of Internal Medicine, University of Minnesota Medical School.)

Four Brucella antigens, consisting of a purified protein, a carbohydrate haptene, a protein-nucleate (brucellergen) and the heat-killed organisms, were used to study dermal hypersensitivity in 174 individuals, eighteen of whom had bacteriologically proved brucellosis. The advantage of using four antigens instead of one to detect hypersensitivity is indicated by the fact that in 45 per cent of those with hypersensitivity at least one of the four skin tests was negative.

Agglutinins for *Brucella* were demonstrated in sixty-five persons, of whom 94 per cent had dermal sensitivity for one or more of the antigens. Dermal hypersensitivity was present in 42 per cent of sixty-nine persons having negative agglutination tests. Of thirty persons with no symptoms, no agglutinins, negative blood cultures and no history of exposure five (or 17 per cent) demonstrated hypersensitivity by the four-test method.

Active infection was demonstrated in fifteen of sixty-two persons with positive agglutinins and positive skin tests. In two cases of *Brucella* endocarditis the carbohydrate test alone was positive until clinical improvement occurred when dermal sensitivity to the other three agents developed. The carbohydrate haptene is unique also in that it produces an immediate erythema and wheal, can be suppressed by benadryl and readily induces the production of agglutinins. Sensitivity to this antigen can be passively transferred. The other antigens produce a delayed reaction. Areas in which any of these antigens provoked inflammation were occasionally reactivated months later upon the exacerbation of symptoms, recurrence of bacteremia or reapplication of skin tests. Violent local reactions with necrosis occurred in 9 per cent of the brucellergen, 4 per cent of the purified protein, 1 per cent of the vaccine and none of the carbohydrate tests. Brucellergen appeared to elicit the greatest number of false positive reactions.

The intensity of the local reaction could be correlated with the titre of agglutinins. Interesting variations in intensity of reaction occur with the stage of the disease of bacteriologically proved cases. The tests have been of doubtful value from a diagnostic viewpoint.

ARTERIOGRAPHY IN THE EVALUATION OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE. *R. G. Smith, M.D. and D. A. Campbell, M.D., Eloise, Michigan.* (From the Department of Surgery, Wayne County General Hospital and Infirmary.)

In a recent study of vascular insufficiency due to arteriosclerosis the usual tests were employed. These included (1) skin and muscle temperatures and the response to autonomic blockade. (2) electrical resistance of the skin. (3) biopsy of ulcers and (4) the common tests of function that determine alteration in color, intermittent

claudication and resting pain. All of these and other tests indicate to some extent the ability of the blood to reach the undernourished tissues of the leg and foot. But these methods are indirect and the information furnished by them may be incomplete or misleading. To these tests we have added arteriography, which appears to be a more direct approach to the estimation of the type and extent of the pathologic changes which have occurred in the arterial system.

The arteriograms of one hundred cases have been studied and classified according to (1) the location and extent of complete obstruction, (2) irregularities of the lumen and (3) the development of collateral circulation.

This method of examination has been carried out by the intern and resident staff and 75 per cent have been satisfactory from a roentgenographic standpoint. Few complications have been noted, the most important of which has been a mild, transient peripheral neuritis in cases in which an extravascular injection had been made. An occasional hematoma developed at the site of injection.

The classification we have adopted has been used as a basis of selection for suitable candidates for lower leg amputation. In addition, though the classification has been used in only a small number undergoing sympathectomy, it appears that it will be helpful in the selection of patients for this operation.

PLEUROPULMONARY MANIFESTATIONS OF AMEBIASIS. *H. T. Langston, M.D. (Introduced by W. G. Maddock), Chicago, Illinois.*

During the past year, ten cases of pleural or pulmonary disease due to amebae have been recognized on the Thoracic Surgery Service at Veterans Administration Hospital, Hines, Ill. The patients were all veterans, but not all of them had seen service in parts of the world where infestation is common. A history of dysentery was recalled by most of them, but known amebic dysentery was not recalled by any of them. They presented themselves with histories and clinical findings resembling those of the common types of pleuropulmonary diseases.

Following the thought of the literature in general, we accept an hepatic abscess as the basic pathologic entity responsible for most of these manifestations, except the isolated lung abscess which may well be embolic. The five

types of lesions described by Ochsner and DeBakey are amplified by us to include the hepatic abscess which ruptures into the subdiaphragmatic space and does not transgress the muscular barrier of the diaphragm.

Demonstration of the organism is difficult from the discharges of these cases (sputum or aspirated fluid) because it represents essentially the liquid material from the hepatic abscess and, therefore, conforms to the usual experience in this regard. The diagnosis in our series of cases was made essentially on the basis of unequivocal response to emetine.

Amebic etiology should be suspected in the differential diagnosis of pleuropulmonary disease when: (1) The clinical course is not typical of the more common entities with which it may be confused. (2) The sputum or aspirated fluid has the appearance of "tomato catsup" or "anchovy sauce," etc. (3) A subdiaphragmatic disorder is present without significant antecedent history of suppurative abdominal disease.

From our experience with these ten patients it is our opinion that pleural or pulmonary amebic disease differs from other types of pleural or pulmonary disease in the following points: (1) Dissemination of the disease by bronchogenic route, even in the presence of copious sputum, is not a significant danger. (2) Communication of a pleural or subdiaphragmatic abscess with the bronchial tree does not necessarily imply the presence of superimposed pyogenic infection.

Since in all instances the response to antiamebic therapy was unequivocal, often even dramatic, non-surgical management is the treatment of choice. Aspiration of liquid accumulations is indicated for relief of symptoms or to expedite recovery, but open drainage should be reserved for control of non-amebic complications.

EVALUATION OF THE ESOPHAGEAL ELECTROCARDIOGRAM IN THE DIAGNOSIS OF HEALED POSTERIOR MYOCARDIAL INFARCTION. *H. B. Burchell, M.D., Rochester, Minnesota.* (From the Division of Medicine, Mayo Clinic.)

Esophageal electrocardiograms are easily obtained. The use of small but heavy electrodes with thin flexible lead wires, together with a direct writing electrocardiographic machine, has facilitated the recording of them. A study of the value of such electrocardiograms in the diagnosis of posterior myocardial scars (previous infarctions) has been carried out in a series of

fifty cases. The fifty cases comprised (1) persons with known previous infarction with and without diagnostic electrocardiographic sequelae, (2) persons with lengthened Q waves in lead III with and without angina pectoris, (3) a few persons with right bundle-branch block with suspected infarction and (4) several patients having anginal pain with the "electrocardiographically vertical" variant of the left ventricular strain pattern. The esophageal electrocardiogram at the ventricular level has shown great variability. In about 10 per cent of cases it retains the form characteristically seen at esophageal levels. When such a form is not present, the electrocardiogram usually simulates the configuration of the left leg unipolar lead, in both "electrocardiographically vertical" hearts or "transverse" hearts. The latter lead (V_F or aV_F) usually is of greater help in evaluation of the significance of prolonged Q waves in derivation III than are esophageal leads. Changes in the esophageal lead that have been most distinctive when myocardial infarction has occurred have been widening and splintering of the initial downward wave and a splintered downward deflection not followed by an R wave. In only one case has a Q wave followed by elevated RT segment been observed. The T wave direction appears to vary independently and has given no help in diagnosis. It appears that an esophageal electrode often continues to be influenced by cavity potential, even when the auricular complex shows no intrinsic type deflection, hence the records obtained usually are not the immediate counterparts of a direct lead from the diaphragmatic area of the ventricle. With the use of the electrodes described, extracardiac potentials produce marked aberrations in the tracings in only a few patients.

STUDIES ON VASOMOTOR TONE IN HYPERTENSION. EFFECT OF TETRAETHYLAMMONIUM ON BLOOD FLOW IN THE EXTREMITIES OF NORMAL AND HYPERTENSIVE SUBJECTS. *H. J. Kowalski, M.D. (by invitation), S. W. Hoobler, M.D., S. D. Malton, M.D. (by invitation), W. G. Pain, M.D. (by invitation), R. H. Lyons, M.D., G. K. Moe, M.D. and J. T. Manning, M.D. (by invitation), Ann Arbor, Michigan.* (From the University of Michigan.)

It is generally agreed that the primary fault in the hypertensive state is an increase in total

peripheral vascular resistance. It has also been shown that there is an increased resistance to blood flow in the extremities in hypertension. The degree to which this elevated resistance is maintained by increased sympathetic tone of preganglionic origin can be estimated by means of the autonomic blocking agent, tetraethylammonium. An increase in blood flow to an extremity following parenteral administration of the drug is associated with a decrease in neurogenic vasoconstrictor tone, and the magnitude of the response is roughly proportional to the initial level of vasomotor tone. Thus, in the feet where vasomotor tone is at a maximum, increases in blood flow after tetraethylammonium are greatest. When vasoconstrictor tone is decreased by warming the body, the response to the drug is lessened. When vasoconstrictor tone is abolished by sympathectomy, the drug no longer increases blood flow.

Consequently, if initial levels of blood flow in hypertensive and normotensive subjects were similar, administration of tetraethylammonium would produce greater increases in blood flow in the former if the increased tone were of sympathetic origin. Response of blood flow to tetraethylammonium in the forearm and in the foot was determined by means of a venous occlusion plethysmograph in twenty hypertensive and twenty-four normotensive patients.

The mean initial blood flow in the foot was 1.7 cc. per 100 cc. of limb per minute for the hypertensives and 2.0 cc. for the normotensive group. Because of wide individual variations, this difference was not considered to be significant. After intravenous administration of 6 mg. per Kg. of tetraethylammonium, blood flow in both the hypertensive and normotensive subjects increased on the average to 4.4 times the resting levels.

The hypertensive group showed a mean resting flow in the forearm of 3.3 cc. per 100 cc. of limb per minute and the normotensive group showed a mean forearm resting flow of 2.9 cc. per 100 cc. of limb per minute, with an average increase to 1.32 and 1.34 times the resting levels after tetraethylammonium, respectively.

The differences were not considered significant and it is therefore concluded that in the extremities of the hypertensive subjects studied there were no alterations in vasomotor tone of preganglionic autonomic origin.

VASCULAR COMPLICATIONS INCIDENT TO
LUMBODORSAL SYMPATHECTOMY. R. D.

AMERICAN JOURNAL OF MEDICINE

Taylor, M.D., A. C. Corcoran, M.D. and I. H. Page, M.D., Cleveland, Ohio. (From the Research Division, Cleveland Clinic Foundation.)

Lumbodorsal sympathectomy is an accepted treatment in some phases of essential hypertension. The frequency of postoperative morbidity and mortality due to vascular causes in such patients is not widely recognized. The incidence of such complications among one hundred hypertensive persons operated upon was surprisingly great. Seventy-nine of these patients had essential hypertension and twenty-one of them were in the malignant phase. The average age was 37.6 years (range twelve to fifty-three years).

Fifteen patients suffered from some form of vascular decompensation in the immediate postoperative period. Among those, three patients with malignant and one with essential hypertension died during or immediately after operation. One patient sustained a myocardial infarction and died after a second attack six weeks later. Acute left ventricular failure and auricular fibrillation occurred on two occasions. The cardiac complications may result from acute coronary insufficiency. One patient developed the signs and symptoms of renal failure, possibly because of the sudden marked reduction of arterial pressure. The remaining seven patients gave evidence of cerebral vascular changes. Minor episodes were attributed to minimal cerebral thrombosis. Major episodes with disorientation or actual psychosis were thought to be due to multiple small thrombi. Of the one hundred patients operated upon, four died presumably directly as a result of operation and eleven showed serious disability.

These observations serve to emphasize that lumbodorsal sympathectomy should not be undertaken lightly and that the risk involved should be recognized.

EFFECT OF SERUM PROTEIN DEPLETION ON
WATER AND SALT EXCRETION AND SENSITIVITY TO PITUITRIN. J. S. Schweppe, M.D. and S. Freeman, Ph.D., M.D. (Introduced by Howard A. Lindberg, M.D.), Chicago, Illinois.

Three dogs were depleted of their serum proteins by a combination of a 4 per cent protein diet and plasmapheresis three to five times per

week. One dog remained as a control throughout the period. Serum protein depletion had the following effects in the dogs studied: (1) The time required to excrete 50 per cent of ingested water increased in all dogs following depletion. This was statistically significant only in one animal. (2) Protein depletion had no effect on the daily twenty-four-hour excretion of chloride. (3) Protein depletion did not appear to alter the twenty-four-hour excretion of chloride after the oral administration of an 0.85 per cent saline solution. (4) During depletion extracellular fluid volume increased slightly in two dogs. (5) The glomerular filtration rate was reduced in all protein depleted dogs. (6) The urinary suppression produced by pituitrin increased markedly in one dog and only slightly in two others. (7) Desoxyeorticosterone acetate in 2 mg./Kg. dosage reduced sodium excretion in all dogs, but had no significant effect on the blood sodium, potassium or chloride levels. Water excretion was not appreciably changed except in one animal which showed a marked suppression. (8) No gross edema or ascitic fluid was present on autopsy. (9) No significant pathologic change was found which could explain the results obtained.

SEROLOGIC TEST FOR STAPHYLOCOCCAL INFECTIONS. *Charles H. Rammelkamp, M.D., Cleveland, Ohio.* (From the Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University.)

Association of potential pathogenicity of staphylococci with the production of an extracellular substance which clots plasma has been widely recognized. In spite of this correlation little is known concerning the rôle of staphylococcal coagulase in the disease process. The existence of antibodies which inhibit the coagulase reaction has not been demonstrated, possibly due to inadequacies of the several techniques employed. In reinvestigating this problem, therefore, it was first necessary to devise a serologic test whereby the factors entering into the coagulase reaction could be controlled. Fraction 1 of the plasma proteins was employed as the indicator system. Staphylococcal coagulase was obtained by growing *Staphylococcus aureus* in tryptose phosphate broth containing 1 per cent human plasma following which the medium was passed through a Seitz filter. A unit was

defined as three times the minimum concentration required to cause the appearance of fibrin in a standard fibrinogen-activator preparation. In determining the neutralizing effect of a serum, a unit of coagulase was placed in contact for a period of ninety minutes with varying dilutions of the serum to be tested, following which a constant amount of substrate, fibrinogen, was added. After three hours incubation the tubes were examined for inhibition of the formation of visible fibrin.

The aforementioned serologic test was employed in a study of sera collected from normal subjects, from patients with staphylococcal infections and from monkeys immunized with cell-free coagulase. The coagulase inhibitory effect of sera from normal subjects varied considerably; many sera exhibited no anticoagulase effect while a few completely inhibited the reaction in dilutions of 1:500 or greater. Acute and convalescent phase sera obtained from patients with staphylococcal infections revealed an increase in the anticoagulase titer in the later blood specimens. These results suggested that coagulase was antigenic. Confirmation was obtained by the demonstration of a rising titer of anticoagulase in the sera of monkeys following immunization with cell-free coagulase. The rôle of this antibody, as well as that of coagulase itself, in the mechanism of infections remains to be established.

PRECARDIAL AND UNIPOLAR EXTREMITY ELECTROCARDIOGRAMS IN FIFTY YOUNG NORMAL MALE ADULTS. *P. H. Noth, M.D. and (by invitation) H. A. Klein, M.D., Detroit, Michigan.*

The Wilson precordial leads (V_3R , V_1-V_6) and Goldberger unipolar extremity leads of fifty young male adults whose hearts were normal by physical and roentgenographic examination were analyzed. The durations of Q, R and S were determined with a Cambridge measuring device. Isolated findings of clinical importance are reported here.

Findings in Precordial Leads. The maximal duration of R (or R-Q) was 0.04 seconds or longer in seven patients, in one of whom it measured 0.045 seconds. Such values are usually considered suggestive of left ventricular hypertrophy. The average of the durations of R (or R-Q) maximal for each patient was 0.034 seconds, which is identical with the value

found for this measurement in sixty-seven pathologically proved cases of left ventricular hypertrophy.

The maximal duration of the QRS complex was 0.114 seconds; for eight subjects it was 0.11 seconds or more and for nineteen subjects, 0.105 seconds or more.

In V_3R , QS deflections occurred in three cases, but otherwise were absent except in one instance in V_1 . Q deflections were not present in leads V_3R , V_1 , V_2 or V_3 . The tallest R in V_3R measured 6.0 mm., in V_1 , 9.0 mm. The duration of R in V_3R varied between 0.001 and 0.031 seconds, averaging 0.017 seconds. In both V_1 and V_2 the maximal values for the duration of R were 0.033 seconds, the average values

0.020 and 0.023, respectively. The T waves in V_3R were inverted in thirty-five, diphasic in two, isoelectric in five, and upright in eight cases. These findings are of interest chiefly for comparison with those in right ventricular hypertrophy and "strain."

Findings in Goldberger Extremity Leads. Duration from onset to nadir of Q in the thirty-four unipolar leads reflecting purely or predominantly left ventricular potentials varied between 0.006 and 0.021 seconds. The depth of Q in these leads varied between 0.5 and 3.0 mm. never exceeding 23 per cent of the height of the following R wave. Thus a Q wave pattern simulating that associated with myocardial infarction was absent.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE WESTERN SECTIONAL MEETING
HELD IN SAN FRANCISCO, NOVEMBER 6, 1947

USE OF HEPARIN IN PRE-ECLAMPSIA. *E. W. Page, M.D., San Francisco, California.* (From the Department of Obstetrics and Gynecology, University of California Medical School.)

During pregnancy the maternal blood is in direct contact with the epithelium of the placenta, an organ which is exceedingly rich in thromboplastin. As shown by Gaifami and many others, saline extracts of the human placenta are lethal to animals when injected intravenously. Schneider has identified this lethal factor as thromboplastin, and suggests that it may be responsible for the fibrin deposition and capillary thromboses observed in the eclamptic woman's liver. Should this be true it might be expected that heparin, a thromboplastin antagonist, would alter the course of pre-eclampsia.

Four women with antepartum pre-eclampsia have been heparinized for periods of seventy-two hours, two by continuous intravenous infusion and two by the intermittent injection of 50 mg. of heparin intravenously every three to four hours. In each case the patient was hospitalized for periods of two to five days in order to use each subject as her own control. In two mild cases the hypertension subsided and proteinuria decreased sharply during the period of heparinization. This apparent improvement continued after stopping the heparin treatment, but the disease recurred in a mild form weeks later in one patient at the time of labor. Two patients with severe cases of pre-eclampsia were treated, one at the seventh and one at the eighth month of pregnancy. In the earlier case the only symptoms were marked hypertension and proteinuria and during heparinization there was no improvement in her condition. A week after cessation of heparin therapy the infant died *in utero* and pregnancy was terminated. In the remaining case of severe pre-eclampsia the outstanding symptom was marked epigastric pain and liver tenderness. During the three days of heparin infusion these symptoms disappeared, the hypertension fell from an average of 190/110 to 160/100 and the proteinuria decreased from 3 to 0.4 Gm. per day. Within twelve hours after cessation of heparin, the epigastric pain re-

turned, blood pressure rose to 200/120 and proteinuria increased. Pregnancy was terminated by cesarean section and a living baby was obtained.

These preliminary results suggest that heparin might be a valuable adjunct in the treatment of pre-eclampsia for the prevention or possibly the alleviation of hepatic damage.

STUDIES ON ERYTHROCYTE PROTOPORPHYRIN, PLASMA IRON AND PLASMA COPPER IN NORMAL AND ANEMIC SUBJECTS. *M. M. Wintrobe, M.D. and G. E. Cartwright, M.D. (by invitation), C. M. Huguley, M.D. and J. Fay, M.D., Salt Lake City, Utah.* (From the Department of Medicine, University of Utah, School of Medicine.)

Values for free erythrocyte protoporphyrin, plasma iron and plasma copper determined in a series of normal adults are presented and analyzed. One or more of these determinations were made in 101 patients with various disturbances in erythropoiesis. In pernicious anemia the erythrocyte protoporphyrin values were normal, the plasma iron normal or elevated and the plasma copper not consistently altered from the normal. In patients with anemia due to a deficiency of iron, the erythrocyte protoporphyrin was found to be high, the plasma iron low and the plasma copper normal or high. Anemia associated with chronic infection was accompanied by a high value for erythrocyte protoporphyrin, a low plasma iron level and increased plasma copper. In nephritis the erythrocyte protoporphyrin was usually elevated, the plasma iron low or normal and the plasma copper variable. Patients with lymphoma and leukemia had a normal or high erythrocyte protoporphyrin, low or normal plasma iron and high plasma copper. In aplastic anemia, plasma iron was elevated. Plumbism was accompanied by high erythrocyte protoporphyrin and normal plasma iron. Myelophthisic anemia was also characterized by a high protoporphyrin content of the erythrocytes. In hemolytic anemia the values were variable. A low plasma copper value was noted in a single patient with hemochromatosis. Thalassemia major was found to be accompanied by a high plasma iron. Mis-

cellaneous diseases including polycythemia, hypothyroidism, multiple myeloma, Laennec's cirrhosis, subacute yellow atrophy of the liver, Banti's syndrome, constitutional hyperbilirubinemia, thalassemia minor and acute prophyria exhibited no abnormal deviations.

ACUTE IDIOPATHIC HYPOPROTHROMBINEMIA.

RESPONSE TO MASSIVE DOSES OF SYNTHETIC VITAMIN K. *R. D. Friedlander, M.D., I. K. Heindl, M.D. (by invitation) and B. G. Anderson, M.D., San Francisco, California.*

The clinical course and dramatic response to vitamin K are described in the case of a middle aged female with apparent idiopathic hypoprothrombinemia. The prognosis was considered to be very grave due to severe respiratory embarrassment as a result of extensive hemorrhage into the deep and superficial tissues of the neck and base of the tongue. Rapid recovery followed administration of large doses of synthetic vitamin K and whole blood. Evidence of hepatic disease was not demonstrable by the usual tests of liver function. Since the patient had been taking small amounts of salicylates, the influence of this drug on the prothrombin time is discussed.

THROMBOPLASTIN REAGENT OF ENHANCED POTENCY AND ITS SIGNIFICANCE WITH RELATION TO THE THEORY OF THE QUICK PROTHROMBIN TEST. *P. M. Aggeler, M.D., T. B. Leake, A.B. (by invitation) and J. Talbot, M.D., San Francisco, California.* (From the Department of Medicine, University of California Medical School.)

Storage of a small quantity of acetone-extracted human or rabbit brain as a thin layer in a glass beaker contained within an evacuated calcium chloride desiccator for periods varying from 47 to 120 days resulted in a marked increase in its thromboplastic potency. Prothrombin times performed with thromboplastin reagent prepared from brains treated in this manner were shorter in normal plasma diluted to 50 per cent of its original concentration than the times obtained with the same plasma in the undiluted state. The results are interpreted as indicating the presence of coagulation-inhibiting substances both in the plasma and in thromboplastin reagents prepared in the usual manner. The results can be explained by the assumption that the increased thromboplastic potency of

brains stored in the manner herein described is due to more complete dehydration resulting in relatively greater insolubility of the coagulation inhibitor contained in the brain.

It is proposed that the prothrombin time obtained with thromboplastin reagents prepared in the usual manner is the net result of a reaction among prothrombin, plasma coagulation inhibitor, thromboplastin and a coagulation inhibitor contained in the thromboplastin reagent. With elimination of the latter inhibitor from the reaction, the effect of dilution of prothrombin to 50 per cent of its original strength is overbalanced by the effect of dilution of the plasma coagulation inhibitor thereby resulting in a faster prothrombin time in the diluted plasma.

COMPARATIVE STUDY OF THE EFFECTS OF ADMINISTRATION OF LARGE DOSES OF HORSE SERUM AND HUMAN ALBUMIN TO RABBITS WITH REFERENCE TO FORMED ELEMENTS OF THE BLOOD, PLASMA PROTEIN CONSTITUENTS AND IMMUNOLOGIC CHANGES. *B. V. Jager, M.D. and R. J. Nelson, M.D. (by invitation), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah Medical School.)

The clinical and experimental observations that serum sickness may result in pathologic lesions simulating those of periarteritis nodosa and acute rheumatic fever suggest that a study of certain hematologic and immunologic aspects of experimental serum sickness in animals might offer useful information.

One group of ten rabbits was given intravenously a single, large dose of horse serum (mixed antigen); a similar group received a single large dose of human albumin (relatively homogenous antigen) while a third group of equal number served as controls. Specimens of blood for various studies were obtained repeatedly from each group during a seven-week period following injection of a foreign protein.

With the exception of a transient lymphopenia which followed injection of albumin or horse serum, the injection of foreign proteins did not lead to significant changes in the packed red cell volume, total and differential leukocyte counts and the reticulocyte response when compared with the control group.

In spite of inherent difficulties attributable to animal variations the rabbits receiving horse

serum showed a moderate increase in plasma fibrinogen and a delayed rise in total globulin and "gamma globulin" (determined chemically). No significant reduction in serum albumin occurred. By contrast no impressive changes occurred in these protein constituents in the animals receiving human albumin. After injection of antigen, circulating precipitinogen persisted much longer and precipitins appeared earlier in the group receiving horse serum than the one receiving human albumin. Antibodies to a globulin fraction of horse serum seemed to develop earlier than antibodies to horse serum albumin.

The total quantitative serum hemolytic complement decreased following administration of horse serum but not after injection of human albumin.

CORRELATION OF LIVER STRUCTURE AND FUNCTION. *L. W. Kinsell, M.D., H. A. Weiss, M.D., G. Michaels, M.D. (by invitation), J. Shaver, M.D. and H. Barton, M.D., Oakland, California.* (From the Department of Medicine, University of California Medical School and the U. S. Naval Hospital.)

Serial liver biopsies have been performed on individuals with acute and chronic liver damage. These patients have been studied simultaneously from the standpoint of liver function as manifested by standard liver function tests as well as by certain other procedures.

It has been found that, in general, acuteness of liver damage is manifested in the biopsy section by phagocytic cell infiltration and that this is usually correlated with the cephalin flocculation test and that chronic, long-standing changes may be correlated with abnormalities of the bromsulphthalein test and with decreased glycogen storage.

COMPARISON OF CHEMICAL DETERMINATION OF SERUM ALBUMIN CONCENTRATION WITH CORRESPONDING ELECTROPHORETIC PATTERNS. *T. B. Schwartz, M.D. (introduced by B. V. Jager, M.D.), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah Medical School.)

Numerous observers have shown that the commonly used sodium sulfate precipitation method

of Howe for the determination of serum albumin concentration gives false high values when compared with those obtained by electrophoresis. In view of the obvious need for a simple, easily executed clinical procedure for estimating albumin concentration in normal and pathologic sera, the results obtained by three precipitation techniques were compared with values obtained by electrophoresis. All four procedures were carried out on aliquots of individual samples of both normal and abnormal sera, the albumin concentration ranging from 17 to 64 per cent in the series of sera tested.

As noted by others the Howe method (21.5 per cent sodium sulfate) yielded serum albumin concentrations that were 4 to 20 per cent higher than those determined electrophoretically. The methanol precipitation procedure described by Pillemer was found to be technically difficult to control and, in pathologic sera, gave results which were consistently lower than the electrophoretic values. Precipitation of serum globulin by saturated magnesium sulfate (Popjak and McCarthy) was found to be a reliable and relatively accurate method for serum protein partition, yielding serum albumin values which correlated closely with those obtained by electrophoresis.

EFFECT OF 2,3-DIMERCAPTOPROPANOL (BAL) ON TOXICITY AND EXCRETION OF GOLD. *W. C. Kuzell, M.D., P. L. Pillsbury, M.D. and S. A. Gellert, B.A., San Francisco, California.* (From the Departments of Pharmacology and Therapeutics and of Medicine, Stanford University School of Medicine.)

Recent clinical observations have shown that 2,3-dimercaptopropanol (BAL) is of value in counteracting the toxic manifestations of gold salts used in the treatment of patients with rheumatoid arthritis. This report presents the results with BAL in protecting white rats against toxic doses of gold sodium thiosulfate and gold chloride and on urinary excretion of gold in rabbits. BAL protects rats against lethal doses of gold sodium thiosulfate given intramuscularly but not against lethal doses of gold chloride given intraperitoneally. Gold chloride is not readily absorbed when given intramuscularly due presumably to severe local tissue destruction. BAL facilitates excretion of both gold sodium thiosulfate and gold chloride given in-

travenously to rabbits in non-lethal doses. *In vitro* BAL reacts readily with gold sodium thio-sulfate to produce a golden yellow precipitate, and with gold chloride to produce a russet brown precipitate thus indicating a high affinity of the thiol groups in BAL for gold, but presumably some tissue-soluble complex is the basis for the antagonistic action in living tissues. The experimental results obtained support the beneficial effects of BAL in clinical manifestations of gold toxicity.

EXCRETION OF UROBILINOGEN IN THE URINE IN PATIENTS SUFFERING FROM CARDIOVASCULAR DISEASES. *F. S. Focht, M.D. and H. T. Hanson, M.D. (introduced by H. H. Hecht, M.D.), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah, School of Medicine.)

Watson and his associates have recently reported that in patients suffering from myocardial infarction, semiquantitative measurements of urobilinogen excreted during a two-hour period revealed increased values for several days following the acute episode. The degree of increment was believed to correlate with the clinical course in such patients.

Repeated tests were performed on a large number of patients suffering from a variety of diseases. The present report deals only with the results obtained in ten instances of myocardial infarction, eleven examples of peripheral vascular thrombosis and emboli and eight patients who were in congestive heart failure not secondary to myocardial infarction.

In congestive heart failure either no rise in urobilinogen excretion in the urine was observed or high values were found on the day of admission, these receding toward normal during the next few days of intensive treatment. In all but one of the patients suffering from myocardial infarction, excretion titers above normal were observed for at least one day. In contrast to patients in congestive heart failure the average maximum excretion occurred on the fourth day following onset of clinical symptoms. It appeared that lower levels were obtained in patients in whom the clinical course and serial electrocardiograms suggested small, non-penetrating infarcts. Peripheral thrombi and emboli were invariably followed by a rise in urine urobilinogen occurring on the average during the first or second day following the onset of clinical signs.

It is pointed out that simple determination of the excretion of urobilinogen in the urine from samples collected during a two-hour period provides another method with which to follow and gauge patients with acute myocardial infarction. It is of no value in differentiating chest pains caused by pulmonary emboli or dissecting aneurysm from those secondary to occlusion of a coronary artery.

PRIMARY CARCINOMA OF THE LUNG. CYTOLOGIC STUDY OF SPUTUM AND BRONCHIAL SECRETIONS. *S. M. Farber, M.D., M. A. Benioff, M.D. and G. Tobias, M.D., San Francisco, California.* (From the University of California Tuberculosis Service, San Francisco Hospital.)

A review of the clinical and pathologic material of 200 cases of primary carcinoma of the lung which came to autopsy at the University of California Medical School and the Stanford Medical School revealed that diagnosis was usually made in the late or terminal stages of the disease. Since primary carcinoma of the lung is bronchogenic in origin, a cough productive of sputum is found in the majority of patients. Examination of sputum or of bronchoscopically removed secretions for neoplastic cells has been reported at various times since the published observations of Hampeln in 1887. Recent advances have been made in proper identification of the cellular elements of the bronchial secretions through use of the Papanicolaou and Traut vaginal smear technic. This method gives an extremely high degree of nuclear and cytoplasmic detail.

This paper presents the cytologic criteria for diagnosis of malignant cells found in the sputum and bronchial secretions. Comparison is made with the cellular components in patients with acute and chronic pulmonary diseases and with the normal epithelial cells, cells from the blood stream and the reticuloendothelial system. Clinical histories are listed when the cytologic examination of the sputum or bronchial secretions established the diagnosis of primary carcinoma of the lung.

USE OF FIBRIN FOAM IN BRONCHIAL STUMP CLOSURE. *M. F. Kepl, M.D. and R. E. Ahlquist, M.D., Spokane, Washington.*

It has been shown by Bailey that final reaction to a large quantity of fibrin foam with

thrombin is less than that to a single black silk suture. After implantation no leukocytic infiltration appears. Fibrin foam is absorbable and controls oozing of tumor beds and cut surfaces of parenchymatous organs.

It is the purpose of this communication to discuss the rationale of the use of fibrin foam as a bronchial plug in the closure of the bronchial stump after lobectomy or pneumonectomy with the anticipation that probably the fibrin foam would act as a scaffolding on which histiocytes and capillary buds would proliferate and hold the bronchial stump, thus preventing the well known phenomenon of "blown bronchus."

A case history is presented in which lobectomy was done for bronchiectasis during which operative procedure it was not possible to cover the bronchial stump with a pleural flap. Fibrin foam, dipped in thrombin, was sutured in place over the closed end of the bronchus which was then irrigated with penicillin-saline solution.

Healing was uneventful. No blown bronchus was evident and the patient returned to work approximately six weeks after the operative procedure. It was believed that the use of fibrin foam in this procedure played a definite role in aiding bronchial stump closure, particularly when the stump could not be covered with pleura.

Editorial

Pain and Dystrophy in the Extremities

IN the last few years there has been renewed interest in the syndromes of pain and dystrophy of the extremities first described by Mitchell, Paget and Sudeck.¹⁻³ These studies present many new descriptive terms,* in evidence that a number of clinical pictures have important features and probably mechanisms in common; and, what is more important, new contributions to underlying physiologic mechanisms.

The most important contributions to the basic physiologic fault have dealt with new concepts of transmission of nerve impulses in previously unrecognized pathways. Skoglund and his associates⁴ have shown by standard physiologic methods that injury to a nerve may establish artificial synapses and result in the transfer of nerve impulses from motor to sensory fibers. Doupe and his associates⁵ independently suggested that in causalgia the essential lesion is one which

permits the passage of impulses in the injured nerve from sympathetic to sensory fibers in which travel centrally, results in pain while distal transmission as antidromic impulses might have vasomotor and trophic effects. They presented this idea mainly as an explanation of pain.

The concept of the pathologic synapse as the essential fault in the pain of causalgia explains remarkably well its distinctive characteristics: initiation by trauma to nerves, relief by block of sympathetics, lack of relief after nerve block distal to point of injury and the peculiarity that causalgic pain is made worse by a number of reactions known to increase impulses in sympathetic nerves of the extremities, such as excitement, a painful pin prick in unaffected parts, a deep breath and adjustments of temperature regulation. Extreme hyperesthesia of an extremity when touched by the examiner, although the patient touches the part without discomfort, is explained in terms of autonomic system reaction to fear rather than as an expression of malingering. In view of the demonstration by Granit and Skoglund that nerve injury may establish an artificial synapse between motor and sensory nerves, it may well be true, as suggested by these workers, that pain on movement may arise in part from abnormal transfer of nerve impulses rather than from actual movement. The pain of phantom limb may be explained by synapses established in a neuroma.

There has been a tendency to assume that exacerbation of causalgic pain with emotional excitement is merely a manifestation

¹ MITCHELL, S. W., MOREHOUSE, G. R. and KEEN, W. W. *Gunshot Wounds and Other Injuries of Nerves*. Chap. 4. Philadelphia, 1864. J. B. Lippincott.

² PAGET, S. M. *Times & Gaz.*, London, p. 531, March, 1864.

³ SUDECK, P. Ueber die akute entzündliche Knochenatrophie. *Arch. f. klin. Chir.*, 147-156, 1900.

* Acute atrophy of bone, traumatic atrophy of bone, traumatic angiospasm, chronic traumatic edema, peripheral trophneurosis, reflex nervous dystrophy, reflex arterial spasm, chronic segmental arterial spasm, reflex dystrophy of the extremities, trophic edema, traumatic osteoporosis, état physiopathique of Vulpian. The multiplicity of descriptive terms currently in use for Mitchell's causalgia and Sudeck's atrophy indicates that none is satisfactory.

⁴ GRANIT, R., LEKSELL, L. and SKOGLUND, C. R. Fibre interaction in injured or compressed region of nerve. *Brain*, 76: 125-40, 1944.

⁵ DOUPE, J., CULLEN, C. H. and CHANCE, G. W. Post-traumatic pain and the causalgic syndrome. *J. Neurol. Neurosurg. & Psychiat.*, 7: 33-48, 1944.

of the patient's neurotic personality. The concept of the pathologic synapse throws light on how lesions of peripheral nerves may put severe stress upon personality. The idea that nerve lesions may contribute to personality disorders need not blind us to the fact that in some cases of chronic pain the principal etiologic factor lies in faulty personality organization. The study of patients with pain and dystrophy of extremities offers a fruitful field for collaboration among psychiatrists, internists and surgeons.

Some of the patients studied by Doupe and his associates, with pain differing somewhat from the pain of classic causalgia, were relieved by nerve block distal to the point of injury. Because of these cases the term dystrophic pain has been introduced with the concept that abnormal transfer of nerve impulses is believed to take place in the periphery rather than in nerve trunks and that the neurologic lesion is a result of defective local nutrition. For those patients Doupe and his associates reverse the usual concept of cause and effect and suggest that pain is a consequence of trophic changes rather than that trophic changes spring from a painful disorder. A mechanism of this sort deserves especial attention by internists because disease of the arteries and veins in the extremities is so common.

There is still great confusion about the mechanisms responsible for local faults of nutrition which are frequently associated with severe and persistent pain in extremities. Such trophic lesions may occur in the absence of pain and it is difficult to quantitate the effects of disuse. There is no doubt that nervous system lesions at different levels may be responsible for vasomotor and trophic disorders: edema, glossy skin, blisters, ulcers, eczema, muscle weakness and atrophy of bone. Bilateral prefrontal lobotomy is frequently followed by pain and edema of the feet and legs; the skin is dry, warm and tender and blisters tend to appear which sometimes form ulcers.⁶ There is a

⁶ ZIEGLER, L. H. and OSGOOD, C. W. Edema and trophic disturbances of the lower extremities complicating prefrontal lobotomy. *Arch. Neurol. & Psychiat.*, 53:

wide difference of opinion as to the meaning of vasomotor disorders associated with pain and dystrophy in extremities. Miller and de Takats⁷ have studied this aspect of the problem with unusual thoroughness and are of the opinion that abnormalities of blood flow are of great importance in the production of trophic disorders. Doupe and his associates minimize the peculiarities of blood flow in extremities with primary injury to damaged nerves, but when there is disease of blood vessels they emphasize the importance of nerve injury caused by defective blood flow. Reider,⁸ whose work is difficult to evaluate because of inadequate details of method, is convinced that hyperemia of the bone marrow is regularly associated with bone atrophy.

The distribution of pain and hyperesthesia in the extremities frequently does not coincide with the area supplied by the injured nerve. Ray and Wolff⁹ studied patients who had had a high thoracic section of the ventral-lateral portion of the cord on one side by applying an intense, noxious stimulus to an analgesic area. The individuals perceived pain on the normally innervated side of the body with such distribution as to indicate that the nerve impulse had spread to the opposite side and to adjacent segments of the cord.

There is good evidence that in some cases of pain and dystrophy we are dealing with a true vicious cycle in which pain induces more pain and tissue injury may favor further local malnutrition. The success in breaking the cycle by procaine injections of sympathetic nerves is frequently spectacular and the benefits outlast the local effect of the drug. This form of therapy deserves earlier and more frequent use in syndromes of severe pain in the extremities.

ROY H. TURNER, M.D.

262, 1945.

⁷ MILLER, DONALD S. and DE TAKATS, GEZA. Post-traumatic dystrophy of the extremities (Sudeck's atrophy). *Surg., Gynec. & Obst.*, 75: 558-582, 1942.

⁸ REIDER, W. Die akute Knochenatrophie. *Deutsche Ztschr. f. Chir.*, 248: 269, 1936.

⁹ RAY, BRONSON S. and WOLFF, H. G. Studies on pain. *Arch. Neurol. & Psychiat.*, 53: 257-61, 1945.

Dynamics of the Left Auricle in Mitral Valve Lesions^{*}

Fluorocardiographic Study

ALDO A. LUISADA, M.D. and FELIX G. FLEISCHNER, M.D.

Boston, Massachusetts

THE effects of mitral valve lesions on the left auricle have been studied by numerous authors using different methods. The fact that in mitral insufficiency blood regurgitates from the left ventricle into the left auricle during ventricular systole was first studied by auscultation. The clinicians of the last century first connected the apical systolic murmur with mitral regurgitation. The observation of a visible and palpable systolic thrust on the right side of the chest due to the expansion of a tremendously dilated left auricle, however, is comparatively recent (Dressler,¹ Ungerleider and Gubner²). Introduction of a compressible balloon and a sound into the esophagus permitted the tracing of volume changes of the left auricle (esophagocardiograms). Taquini³ and Puddu and Sibilla⁴ described a positive wave of short duration at the beginning of ventricular systole in cases of mitral insufficiency.

More accurate observations of motor changes of the left auricle have been made roentgenologically. Fluoroscopy may permit observation of a systolic expansion of the left auricle, especially if the esophagus is filled with barium. Roentgenkymography yielded characteristic records of the left auricle in either of the following conditions: (1) In cases in which the left auricle was so markedly enlarged that it formed a major portion of either the right or left cardiac silhouette permitting its pulsation to be

recorded in the posteroanterior view and (2) in other cases in which the pulsations of the left auricle were best recorded in the right or left oblique position with the esophagus filled with barium.

Although various observations have been reported in scattered publications and textbooks of roentgenology (Cignolini,⁵ Roesler,⁶ Gubner and Ungerleider² and Schwedel⁷), the most thorough kymographic study of the left auricle was published only recently by Heim de Balzac and Pannier.⁸

This paper will discuss the use of fluorocardiography in the study of the dynamics of the left auricle in mitral valve lesions. It is believed that fluorocardiography provides the most accurate tracings and we have utilized it in an investigation of all such cases coming under our observation.

TECHNIC

Henny, Boone and Chamberlain^{9,10} described a roentgenologic method which they called electrokymography. A modification of this technic (Luisada, Fleischner and Rappaport¹¹) has been employed in this study. We proposed the more descriptive term of *fluorocardiography* which will be used in this presentation. A Sanborn apparatus for fluorocardiography connected with a Stethocardiette has been used in order to record simultaneously the cardiac sounds and the pulsations of the various components of the cardiac silhouette. The

^{*} From the Medical Service and the Department of Radiology of the Beth Israel Hospital, Boston, Mass.

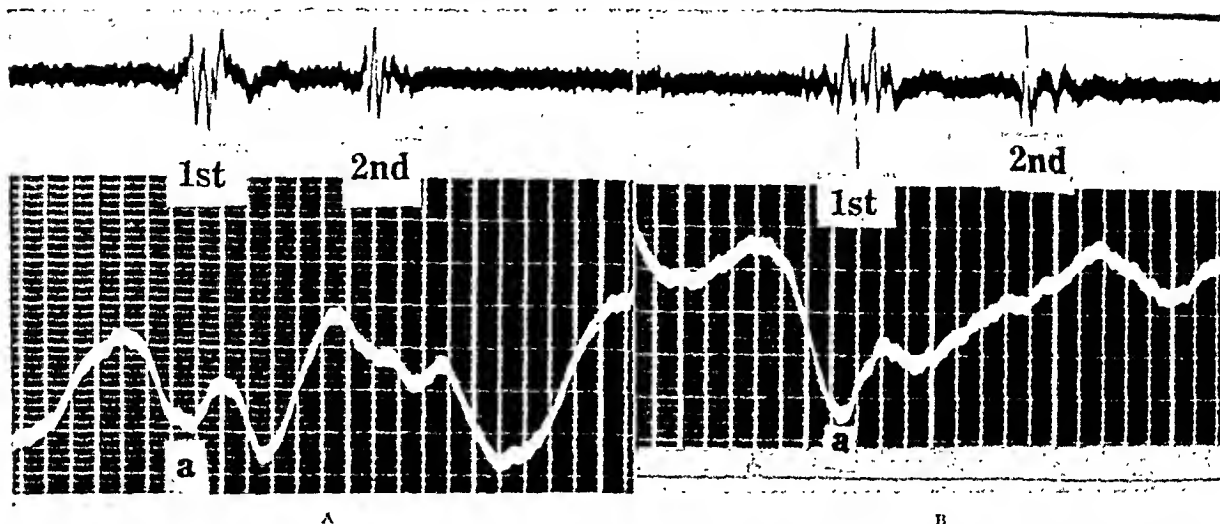


FIG. 1. Tracings of the left auricle in two normal male subjects aged twenty-two; right oblique position. A, a deep negative ventricular wave follows the auricular wave; n, a sharp negative auricular wave is present; the ventricular wave is less marked; a, indicates the auricular wave.

phonocardiograph was used not only as timer but also to study the heart sounds and murmurs. The technic used has been described in detail in a previous paper.¹¹ The present study deals only with observations of the left auricle.

This study includes twenty-seven examinations made on clinical patients. At first only patients definitely diagnosed by clinical means were studied; then, having observed a series of what were thought to be characteristic tracings, we also studied a few patients in whom the diagnosis was not established by ordinary clinical methods. All the patients studied included five with combined mitral and aortic lesions of rheumatic etiology; ten with double mitral defects of rheumatic etiology; three with mitral insufficiency and no clinical evidence of stenosis; two with mitral stenosis and no clinical evidence of regurgitation; two with complex cardiac lesions (probably of both rheumatic and congenital nature; one of them had Lutembacher's syndrome); one with arteriosclerotic heart disease with evidence of mitral regurgitation (apical systolic murmur) and four with clinical diagnosis of interventricular septal defect and a loud systolic murmur.

All patients were studied by means of physical examination, electrocardiography, phonocardiography and roentgenology be-

fore the fluorocardiographic study was undertaken. In most of the patients the three following sitting positions were employed: (1) The contour of the left auricular appendage was traced with the patient in a posteroanterior position, rotated 10 degrees to the left anterior oblique; (2) the contour of the left auricle was traced in the left anterior oblique as well as the right anterior oblique and (3) in addition, a densogram of the left auricle in one of the oblique positions was recorded in some of the patients.

OBSERVATIONS

As described in a previous paper¹² the tracings recorded over the left auricle in normal subjects present a typical pattern (Fig. 1) consisting of: (1) A sharp, presystolic, negative wave whose trough coincides with the initial vibrations of the first sound. (2) A smaller negative wave during ventricular systole. (3) A less constant, early diastolic collapse which may merge with the following presystolic wave (especially if there is tachycardia). An upward wave, occurring during the first sound, separates the presystolic from the systolic negative wave. The ascending limb of the latter often shows a gentle slope during late systole, due to the gradual filling of the auricle, and reaches its maximum height at the end of the second sound when a specific vibration

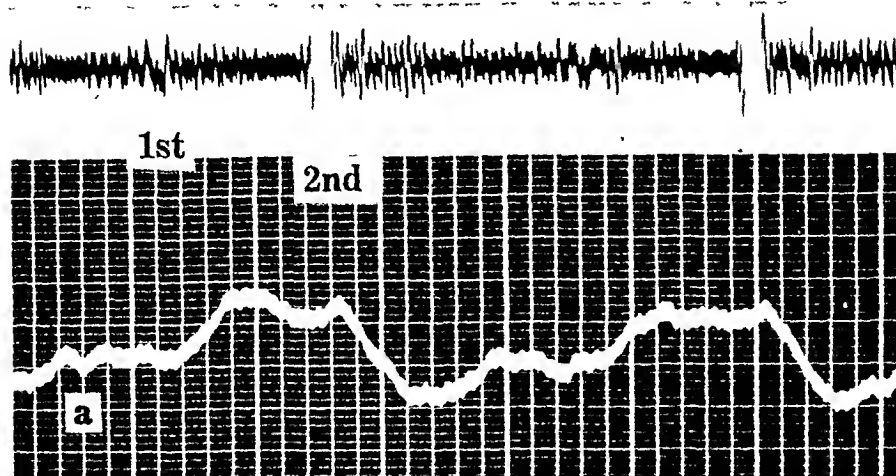


FIG. 2. Tracing of the left auricle in a thirty-two year old woman; mitral valve lesion; small auricular wave (a) followed by positive plateau during ventricular systole.

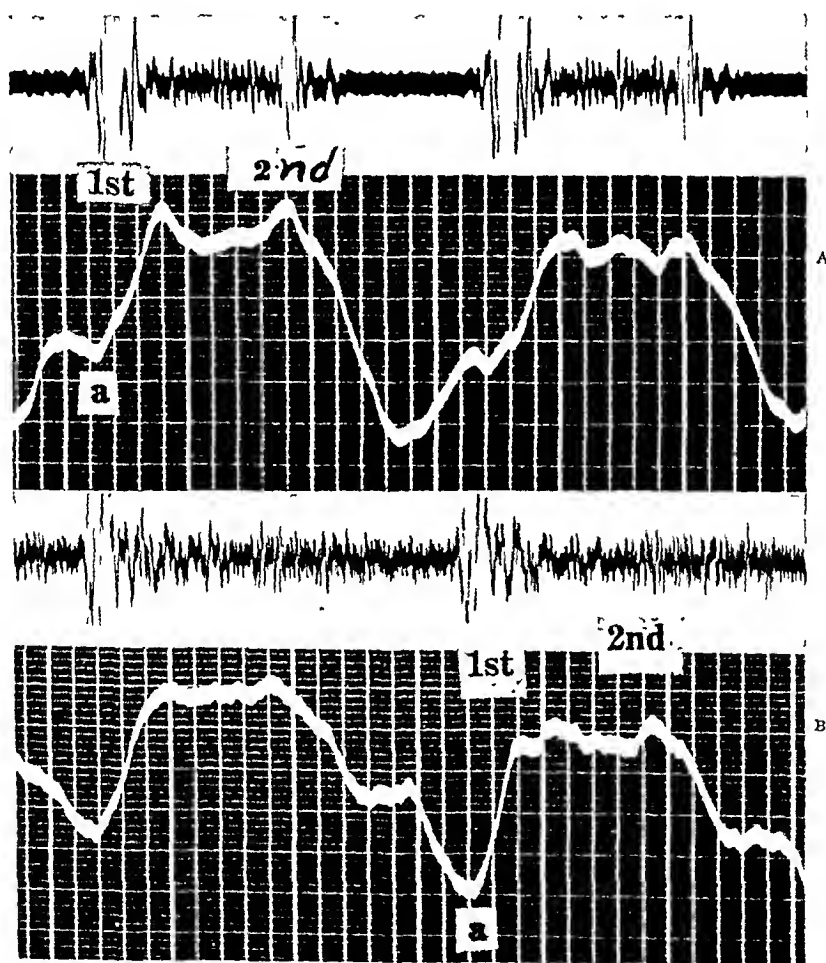


FIG. 3. Tracings of the left auricle in two patients with lesions of the mitral valve and sinus rhythm. A, a fifteen year old girl with a slight mitral lesion; long systolic murmur; deep negative auricular wave followed by positive plateau during ventricular systole. B, a thirty-five year old woman with mitral and aortic lesions; deep negative auricular wave followed by positive plateau during ventricular systole. Both tracings were recorded in the left anterior oblique position.

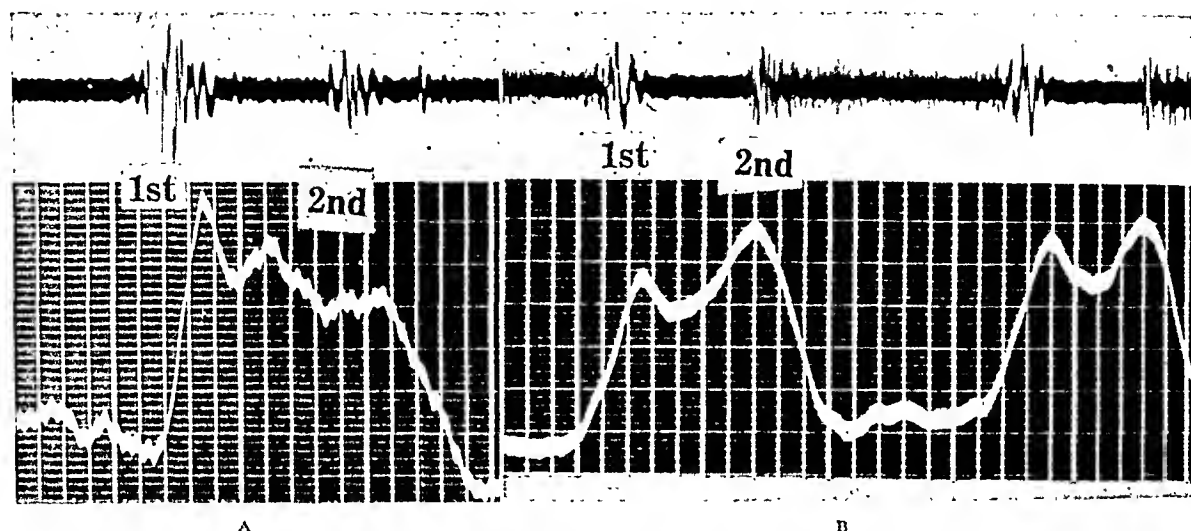


FIG. 4. Tracings of the left auricle in left oblique position in patients with mitral valve lesion and auricular fibrillation; high positive plateau; no evidence of auricular contraction. A, a forty-two year old woman with no systolic murmur audible and an opening snap of the mitral valve; n, aortic and mitral lesions.

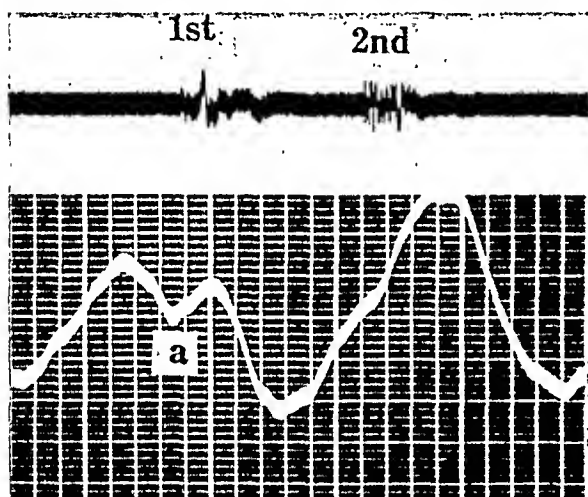


FIG. 5. Tracing of the left auricle showing normal configuration in a man of twenty-four with clinical diagnosis of interventricular septal defect.

marks the opening of the mitral valve (Rappaport and Sprague).¹³

Patients with Mitral Valve Lesions without Auricular Fibrillation. This group included sixteen observations made on thirteen patients; in fifteen observations there was a normal sinus rhythm and in one, nodal rhythm. In ten of the patients a typical pattern was observed which may be analyzed as follows: (1) The presystolic negative wave, evidence of auricular contraction, is present. It may be small, irregular in shape or barely visible. (Fig. 2.) (2) During ventricular systole a flat positive wave shaped as a "plateau" is present. It is

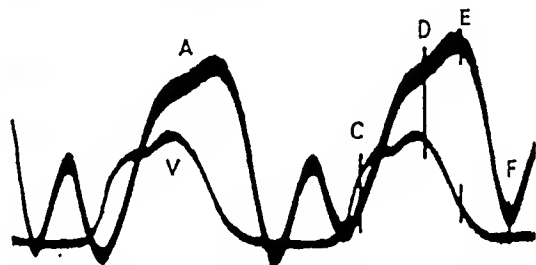


FIG. 6. Curves showing relation between left atrial volume (A) and left ventricular pressure (v) during experimental mitral regurgitation. Atrial volume increases insignificantly during isometric contraction ending at c, augments markedly during ventricular ejection terminating at v, and is continuous during isometric relaxation terminating at E. (From Wiggers' *Physiology in Health and Disease*. Courtesy of the author and of the Lea and Febiger Co.)

identical in shape and time relationship with that observed in patients with auricular fibrillation. (Fig. 3.)

The other three patients in whom a normal or nearly normal pattern was observed, were studied earlier and incompletely, i.e., only in one or two positions. Inasmuch as the aforementioned typical pattern does not necessarily present itself in all positions, the negative findings in these patients may be explained on this basis.

Patients with Mitral Valve Lesions and Auricular Fibrillation. This group included ten patients; in nine of them a typical pattern (Fig. 4) was observed which had the following characteristics: (1) Absence of the presystolic auricular wave and (2) presence of an abnormal positive wave

during ventricular systole. This has the form of a quadrangular or rectangular "plateau." It resembles tracings of intraventricular pressure as observed in animal experiments. If an early diastolic collapse is present, the tracing consists of the systolic plateau, the

interfere with the appearance of the plateau. (2) Patients with mitral stenosis and no evidence of insufficiency (no systolic murmur) also present a typical plateau. (3) The plateau is typical in patients with sinus rhythm as well as in those with auricular

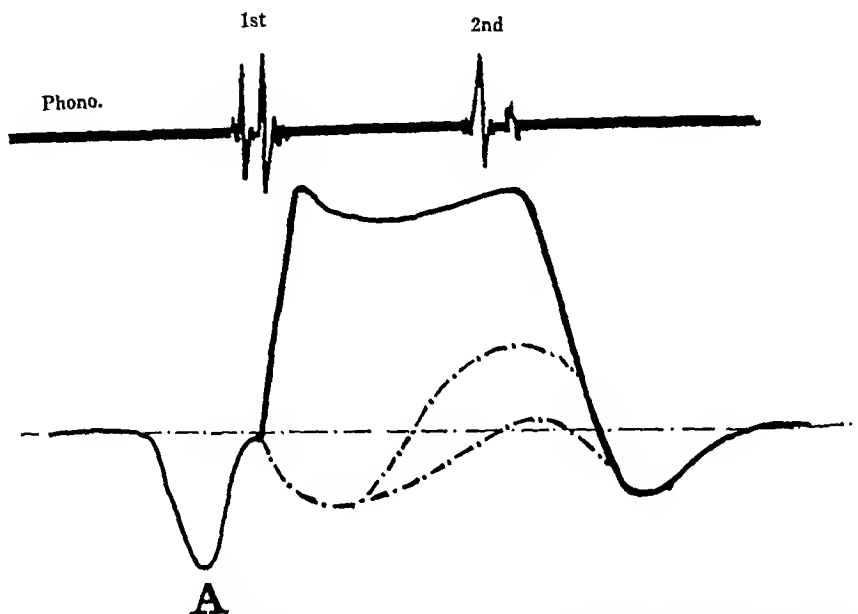


FIG. 7. Sketch of the tracing of the left auricle in a case of mitral lesion with sinus rhythm. The thin dotted line represents the arbitrary base line; the heavy dotted line represents normal tracings during ventricular systole.

descending limb of which reaches further down as it merges with this collapse.

The only patient in whom this plateau was not found probably had a combined rheumatic and congenital lesion (mitral lesion plus septal defect) and, moreover, was not completely studied. Patients with an interventricular septal defect presented normal left auricular tracings. (Fig. 5.)

In summary, of twenty-three patients with mitral valvular disease, nineteen presented a typical pattern, differing from the normal, characterized by a positive plateau during ventricular systole. Correlation of the clinical diagnoses, the phonocardiographic findings and the fluorocardiographic tracings leads to the following conclusions:

(1) Patients with mitral regurgitation or a double mitral lesion present a typical positive plateau which is especially prominent in the presence of auricular fibrillation. Associated aortic valvular lesions do not

fibrillation. (4) Patients clinically diagnosed as having an uncomplicated interventricular septal defect do not show any abnormal pattern in the tracing of the left auricle.

COMMENTS

A typical fluorocardiographic tracing of the left auricle in patients with mitral valvular disease is produced by the continuous regurgitation of blood from the left ventricle into the left auricle during ventricular systole and is present in patients with sinus rhythm or auricular fibrillation. It consists of a rectangular, positive "plateau" resembling the classical experimental tracing of intraventricular pressure. This finding is not unexpected as it conforms with tracings obtained under experimental conditions of mitral regurgitation (Wiggers,¹⁴ Fig. 6) and with clinical esophagocardiograms.^{3,4} Moreover, it has been recorded by means of roentgenkymograms

made on patients with severe mitral lesions and a large left auricle (Cignolini,⁵ Heim de Balzac and Pannier⁸).

It must be noted, however, that there are contradictions in these earlier studies. While the experiments on animals demonstrate

been stated⁸ that a loud systolic murmur due to a mitral lesion may be present without a typical plateau revealing the regurgitation. While this possibility cannot be ruled out, we have not found any satisfactorily studied case which confirms this

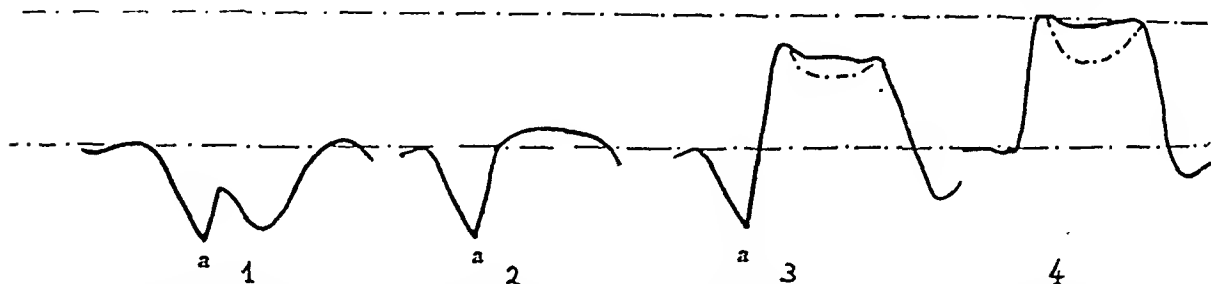


FIG. 8. Schematic tracings of the left auricle in mitral lesions: (1) normal; (2) initial neutralization of systolic collapse; (3) sinus rhythm, positive systolic plateau preceded by auricular contraction; (4) auricular fibrillation; positive systolic plateau, no trace of auricular activity.

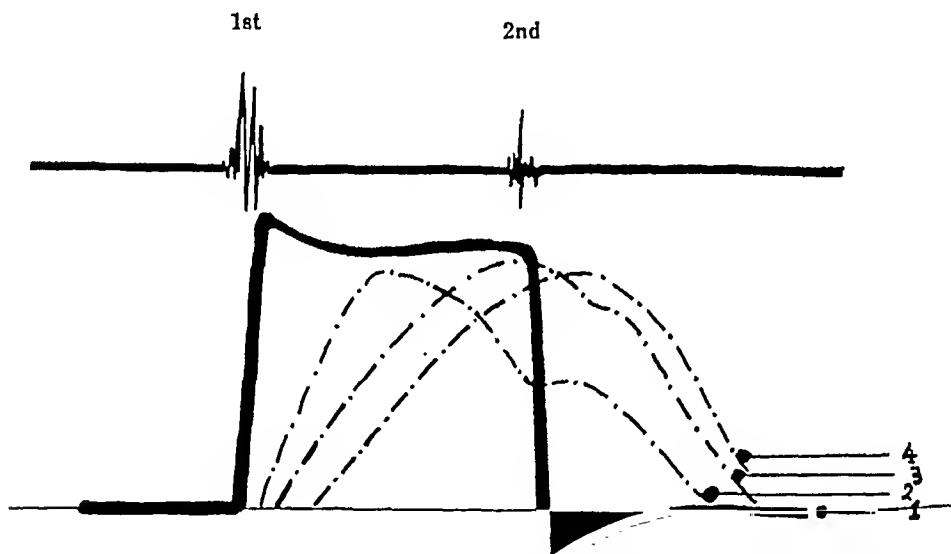


FIG. 9. Sketch showing differentiation of the positive plateau (1), from the pulsation of the pulmonary artery (2), of the hilar vessels (3) or the lung (4). Shape and relationship of the waves to the heart sounds are different.

regurgitation during and after the ejection period,¹⁴ clinical esophagocardiograms showed regurgitation only at the beginning of systole.⁴ In our tracings the regurgitation appears to be continuous, starting at the beginning of the tension period and continuing until after the opening of the mitral valve, i.e., after the end of the second sound. These findings, therefore, conform with the results of animal experimentation.

Classical roentgenkymography⁸ demonstrated the occasional occurrence of severe regurgitation without a systolic murmur; the present studies confirm this. It has also

observation. A typical pattern of regurgitation was found in all patients with mitral regurgitation in whom sinus rhythm was present, the left auricle was only moderately enlarged and no auscultatory or phonocardiographic evidence of mitral stenosis was present. (Fig. 8.)

Another abnormal feature may be found in tracings from patients with mitral lesions and sinus rhythm. (Fig. 2.) This consists of an abnormal form and depth of the auricular wave which is small, irregular and often difficult to visualize. This abnormality may be attributed either to slow

emptying of the left auricle because of severe mitral narrowing or to weak left auricular contraction caused by muscular damage in the left auricle.

By recording tracings of the left auricle in the oblique positions, superimposition of other structures, such as the pulmonary artery, the hilar vessels or the aorta is avoided. However, misinterpretation, possibly resulting from a summation of waves, can be obviated only by careful observation of the typical form of the specific waves and their relationship to the heart sounds. (Fig. 9.)

In conclusion, the fluorocardiogram of the left auricle in mitral valvular disease typically demonstrates a positive plateau (regurgitation) during ventricular systole. This is easily identified whenever there is auricular fibrillation and thus it may be of diagnostic value in the absence of an apical murmur. In patients with sinus rhythm the plateau wave is, however, of diagnostic value only if it is marked because of the absence of a definite base line. Hence only marked evidence of systolic elevation can be accepted as proof of a pathologic disorder. On the contrary, in the presence of moderate regurgitation the resulting elevation being only slight, it merely neutralizes the negative systolic wave or produces a slight rise which may be mistaken for the normal rise which occurs after the negative presystolic wave. (Figs. 8(2).) This finding, therefore, cannot be accepted as definite evidence of regurgitation.

Our findings indicate that in the patients studied mitral stenosis was always accompanied by regurgitation.

SUMMARY

Fluorocardiographic tracings of the left auricle were recorded in twenty-three patients with lesions of the mitral valve. The patients were about equally divided into two groups: one with sinus rhythm and the other with auricular fibrillation.

A typical pattern was found in nine of ten patients with fibrillation and in ten of thirteen of those with sinus rhythm. This consists of a positive *plateau* which is

evidence of expansion of the left auricle during ventricular systole because of regurgitation.

A description of the distinctive features of this pattern is given.

Another variation, consisting of abnormalities in shape and depth of the presystolic auricular wave, is found in certain patients with sinus rhythm and is explained as the result either of severe narrowing of the mitral valve or structural lesion of the left auricular wall.

The practical diagnostic value of these graphic signs is discussed.

Possible existence of a pure mitral stenosis, not accompanied by mitral insufficiency, was not demonstrated in the present study.

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Application of Microplethysmography to the Diagnosis of Patent Ductus Arteriosus and Coarctation of the Aorta*

RAYMOND S. MEGIBOW, M.D.† and SERGEI FEITELBERG, M.D.

New York, New York

RECENT developments in the surgical treatment of congenital heart disease have increased the practical importance of accurate anatomic diagnosis. This has been accomplished in part through development of more precise diagnostic criteria, and by use of specialized technics such as angiocardiography and direct catheterization of the heart.¹⁻⁴ In spite of these advances a small percentage of diagnostic errors persists.

It is the purpose of this report to relate observations made with a relatively new technic which led to the formulation of new diagnostic criteria in the preoperative study of patients with suspected patent ductus arteriosus and coarctation of the aorta.

METHODS

A direct ink recording microplethysmograph constructed by one of us (S. F.) has been utilized in all investigations. Exact details of construction are being published separately. Sensitivity is adjusted (by operating a control knob) to give a deflection of 10 to 20 divisions for a volume change of 20 mm.³, full chart scale being equal to 50 divisions. Calibration may be checked manually at any time or automatically every ten minutes by introducing a volume change of 20 mm.³ into the system. The response of the pen is linear within 5 per cent over the 50 divisions. Noise level is less than $\frac{1}{4}$ division corresponding to a volume change of less than 0.25 mm.³ The frequency response is 5 cycles/second. The timing is automatic.

* From the Clinical Services and the Physics Laboratory of The Mount Sinai Hospital, New York, N. Y. Presented in part at the International Pediatric Congress August, 1947. Read in part by title at the meeting of the American Heart Association June, 1947.

† Fellow in Medicine, Rosenstock Memorial Foundation.

Whenever possible, the procedure was carefully explained to each patient beforehand. All tracings were obtained with the patient reclining comfortably on a couch. Psychic stimuli were kept at a minimum since they exert a profound effect upon the plethysmogram.⁵ No effort was made to control temperature and humidity as long as the patient was not unduly chilled or warmed. Actual tracings were obtained by applying a plastic capsule to the fingers or toes according to a method previously described.⁶ At least one recording was obtained on each patient preoperatively. In a number of instances the effects of nitroglycerin on the plethysmogram were observed. Whenever possible, plethysmograms were obtained after operation and were compared with the preoperative tracings. In a number of patients angiocardiograms were included in the diagnostic study. Electrocardiograms and in a number of instances phonocardiograms were also made available for study in these patients. All subjects underwent careful physical examination, particular attention being given to the character and transmission of the cardiac murmurs and to the arterial pressure.

RESULTS

The normal plethysmogram has been adequately described by Neumann et al.⁷ (Figs. 1 and 2.) It is characterized by four distinct types of volume fluctuation: (1) a wave synchronous with the heart beat, (2) slower undulations which are induced by respiration and are more distinct in the fingers than in the toes, (3) much slower and larger volume changes, termed alpha

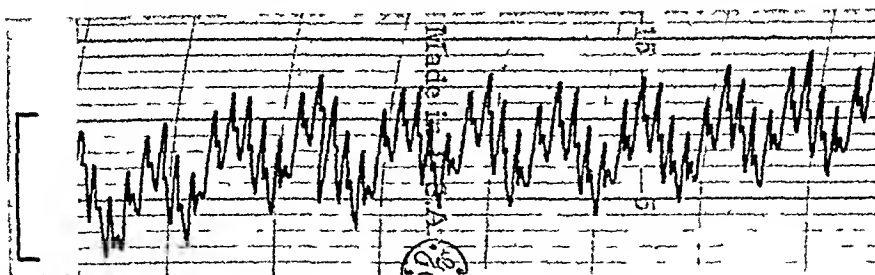


FIG. 1. Plethysmogram from finger of a normal subject. Note the sharp apex, the distinct diastolic notch and the well developed respiratory fluctuations (Ordinates equal 5 seconds. Calibration to left of each figure indicates a volume change of 20 mm³).

waves, induced apparently by phasic or aphasie changes in sympathetic tone and finally (4) waves of even slower frequency and greater amplitude than the alpha waves, designated beta and gamma waves, the genesis of which is not understood.

The basic component of the plethysmogram, the volume pulse, normally exhibits a characteristic pattern. The apex is sharp and pointed; the systolic rise is more acute than the diastolic fall; the diastolic notch is clearly discernible, located usually about the mid-portion of the diastolic limb and is relatively constant in position from beat to beat. Both contour and volume pulse amplitude remain relatively constant during any period of observation unless the subject is exposed to various stimuli.

This standard configuration is markedly altered by the presence of patent ductus arteriosus. (Fig. 3.) The changes consist of distinct blunting, broadening or flattening of the apex, loss in the normal slope difference of systolic ascent and diastolic descent, the limbs tending to become equal, and the diastolic notch is found to vary in position with successive pulsations; usually it is located on the diastolic limb close to the apex, but on rare occasions it may be noted in a high anacrotic position. Finally, small but significant variations in general contour and amplitude are apparent from moment to moment. No significant alterations in respiratory, alpha, beta or gamma deflections have been found.

During the past eighteen months plethysmograms have been obtained in twenty-six patients clinically suspected of having

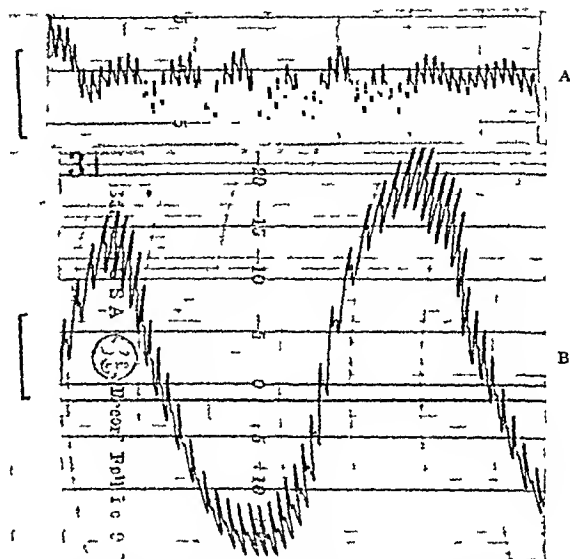


FIG. 2. Plethysmograms from a normal subject. A, from the second left finger, B, from the left great toe. Note that the respiratory fluctuations are well developed in the finger and indiscernible in toe, while the uncorrected volume pulse amplitude and alpha deflections are greater in the toe than in the finger.

patent ductus arteriosus. The essential clinical data are presented in Table 1. A plethysmographic pattern considered typical of patent ductus was found in twenty-three subjects and a questionable or equivocal tracing in one.

In the following paragraphs the data obtained by means of plethysmography are compared with the observations made at operation and with those made by angiocardiology, electrocardiography, auscultation and sphygmomanometry.

Operative Findings. Seventeen patients were subjected to exploratory thoracotomy. One of these patients (J. O'C) had the tetralogy of Fallot and had undergone a

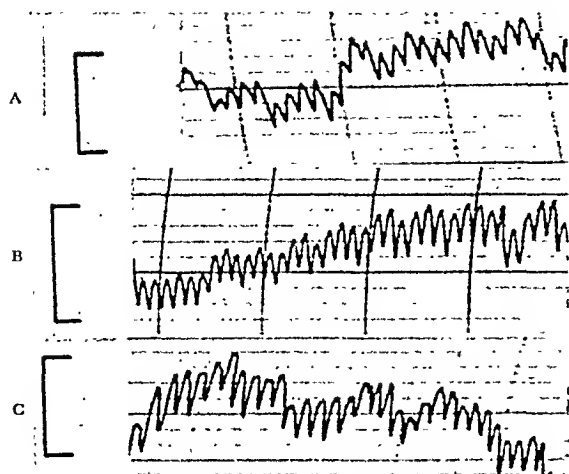


FIG. 3. A to C, plethysmograms from the finger in three instances of patent ductus arteriosus. Note the blunt apex, the absence of or barely discernible notch and the loss of slope variation with systole and diastole.

Blalock-Taussig operation at another hospital. The plethysmogram obtained three and one-half months after this procedure demonstrated the typical pattern of patent ductus. Of the remaining sixteen patients patent ductus was found in fifteen and patent interauricular septum in one. The plethysmogram in this latter case revealed no significant abnormalities. Characteristic plethysmograms were found in fourteen of the remaining fifteen patients. In the one instance in which a discrepancy existed between the plethysmographic and operative findings (the authors disagreed on interpretation) a relatively small ductus was found and ligated. Oxygen determinations of aortic and pulmonic arterial blood at the time of operation disclosed normal

TABLE 1

ESSENTIAL CLINICAL AND LABORATORY FINDINGS IN TWENTY-SIX SUSPECTED INSTANCES OF PATENT DUCTUS ARTERIOSUS

Name	Age	BP	Murmur	ECG	Angiocardiogram	Plethysmogram	Operation	Diagnosis
P. P.	9	114/50	T	P	P	Lig.	P.D.
R. K.	31	122/82	T	N	P	P	Lig.	P.D.
E. deV.	8	110/70	N.T.	RVP	P	P	Lig.	P.D.
R. M.	7	80/40	T	N	E	P	Lig.	P.D.
M. F.	25	138/68	T	N	N.D.	P	Lig.	P.D.
J. L.	6	110/70	T	N.D.	P	Lig.	P.D.
C. A.	11	126/60	T	N.D.	P	Lig.	P.D.
C. O.	10	108/78	T	N.D.	P	Lig.	P.D.
M. K.	15	120/50	N.T.	N.D.	P	Lig.	P.D.
M. J.	3	120/76	T	N	N.D.	P	Lig.	P.D.
N. K.	4	104/68	T	N.D.	P	Lig.	P.D.
I. G.	6	110/60	T	N.D.	P	Lig.	P.D.
W. S.	28	100/60	N.T.	N	N.D.	P	Lig.	P.D.
M. K.	7	118/58	N.T.	N	N.D.	P	Lig.	P.D.
H. B.	6	90/40	T	P	P	N.D.	P.D.
B. U.	15	104/60	N.T.	N	P	P	N.D.	P.D.
C. K.	11	118/20	T	N.D.	P	N.D.	P.D.
T. C.	13	120/48	N.T.	N	N.D.	P	N.D.	P.D.
J. C.	4	90/26	T	N	N.D.	P	N.D.	P.D.
P. S.	32	124/68	T	N	E	P	N.D.	P.D.
M. H.	15	130/65	T	LAS	P	E	Lig.	P.D.
S. S.	21	126/46	N.T.	T in 1, 2, 3	P	P	N.D.	P.D.
S. B.	6	90/50	N.T.	RVP	P	P	Tetralogy of Fallot and patent ductus
J. O'C.	10	122/64	N.T.	RVP	N.D.	P	Post-Blalock operation
J. H.	2	108/64	N.T.	N	N.D.	N	Subaortic stenosis
B. M.	6	112/70	N.T.	High voltage	P	N	Interauricular septum

T—Machinery murmur
 N.T.—Not typical
 P—Positive
 E—Equivocal
 N.D.—Not done

P.D.—Patent ductus
 Lig.—Ligation of patent ductus
 N—Normal
 RVP—Right ventricular preponderance
 LAS—Left axis shift

relationships. This may possibly indicate that physiologically insignificant amounts of blood were being shunted through the ductus, and may therefore serve to explain the difficulty in interpreting the plethysmographic changes in this patient.

Angiocardiography. Angiocardiography has proven of inestimable value in diagnosis of various forms of congenital heart disease. A characteristic angiocardiogram has been described in cases of patent ductus.¹ Angiocardiograms were obtained in eleven patients and a characteristic infundibulum was demonstrable in nine. In the remaining two the findings were considered suggestive. In this same series a diagnostically significant plethysmogram was found in nine patients. The two patients with a negative or doubtful plethysmogram had positive angiocardiograms. They were subjected to exploratory thoracotomy and, as mentioned previously, an interauricular septal defect was found in one and a relatively small ductus in the other. In the two patients with suggestive angiocardiograms, plethysmograms considered typical of patent ductus were obtained. One of these two patients was operated upon and a patent ductus found and ligated.

Electrocardiography. It is well known that the electrocardiographic pattern is usually normal in patients with patent ductus. The presence of right or left ventricular preponderance either speaks against diagnosis of patent ductus or indicates coexistence of other cardiac defects.^{4,8} In general, our experiences confirm these observations. Of seventeen patients in whom electrocardiograms were available for analysis the tracings were normal in eleven. Typical plethysmograms were obtained in ten of these eleven patients. The exception revealed an anacrotic notch and systolic plateau on the pressure pulse tracing, slight left ventricular enlargement on fluoroscopy and a loud systolic murmur over the upper portion of the sternum on phonocardiography. Subaortic stenosis was considered the most likely diagnosis. Abnormal electrocardiograms were found in the remaining

six patients. There were three instances of right ventricular preponderance, two in patients with the tetralogy of Fallot. One of these, previously described, had undergone the Blalock procedure. In the other the existence of concomitant patent ductus was entirely unsuspected until demonstrated by the plethysmogram and subsequently by the angiocardiogram. There was one patient, found to have an interauricular septal defect, in whom the electrocardiogram revealed high voltage QRS complexes in the limb leads. The plethysmogram was normal in this individual. One electrocardiogram revealed a left axis shift; this was found in the patient described previously in whom the plethysmogram was questionable and in whom operation disclosed a small ductus. The last patient in this series revealed striking electrocardiographic abnormalities characterized by tall notched P waves, QRS complexes of high voltage and inversion of the T waves in the standard leads. The pulse pressure was high. The phonocardiogram indicated the existence of a loud systolic murmur over the entire precordium with a faint diastolic component limited to the pulmonic area. The plethysmogram was characteristic of patent ductus and the angiocardiogram presented no abnormalities other than the characteristic infundibulum.

Blood Pressure. The influence of patent ductus on systemic arterial pressure is fairly well shown in our series. In fifteen cases there was a pronounced and in two cases a slight increase in pulse pressure produced primarily by a low diastolic level. Systolic and diastolic pressures were well within the normal range in the remaining seven patients. Typical plethysmograms were obtained in this latter group and operation subsequently disclosed a patent ductus in each instance.

Murmurs. The classical machinery murmur was present in fifteen of the twenty-six patients. Of the eleven in whom the murmur was absent, two were found to have a harsh, rough precordial systolic murmur associated with a faint (grade II) diastolic

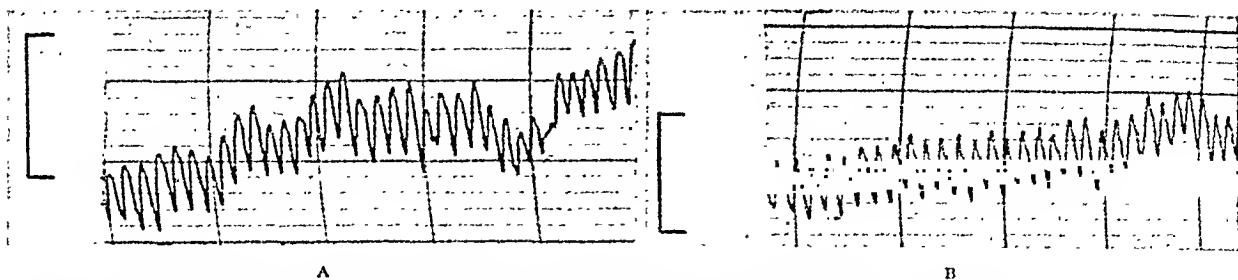


FIG. 4. A and B, plethysmograms from the same finger before and after ligation of a patent ductus. Note that in the postoperative tracing the apex is sharp and the dicrotic notch is quite distinct.

murmur over the pulmonic area. A systolic murmur of grade III and IV intensity, maximal over the second left interspace, was audible in two patients. In two instances, both with tetralogy of Fallot, exact significance of the auscultatory findings could not be properly evaluated. In the remaining five, systolic murmurs of varying intensity, usually of grade IV, were found over different parts of the precordium. Thus nine of the twenty-four patients in whom a diagnosis of patent ductus was substantiated either by operation or additional diagnostic criteria failed to present the machinery murmur. Plethysmography indicated the nature of the defect in eight of this group and gave uncertain results in the ninth patient.

Plethysmogram Following Closure of Patent Ductus. In our series sixteen patients were subjected to exploratory thoracotomy for closure of a suspected ductus. In fifteen a patent ductus was found and ligated. In the remaining instance, described previously, a patent interauricular septum was found. Plethysmograms were obtained in all fifteen patients seven to fourteen days postoperatively; in eleven the tracings had become normal as judged by the appearance of a sharper apex, and a distinct dicrotic notch constant in position. (Fig. 4.) Fluctuations in contour and volume amplitude tended to disappear, and the difference in the slope of the systolic and diastolic limbs became more pronounced. One patient examined two weeks after operation failed to disclose any significant plethysmographic alteration; reexamination a year later revealed an entirely normal tracing. In the three remaining patients, plethysmograms ob-

tained within two weeks after operation were substantially the same as the preoperative records although in each, closure of the ductus had been accomplished successfully as was shown by the disappearance of the characteristic murmur and by a decrease in the pulse pressure. Apparently the plethysmogram does not become normal immediately after operation in all cases. This seems to be in agreement with the well known postoperative persistence of a pulmonic systolic murmur of varying intensity, and of the characteristic infundibulum on the angiocardigram. Such findings may serve to indicate the continued presence of certain vascular alterations which may account for the continued postoperative presence of an abnormal plethysmographic pattern.

COMMENTS

As yet the circulatory factors underlying production of the characteristic plethysmographic pattern in patent ductus arteriosus are not clearly understood. An increase in pulse pressure plays no significant rôle. This is indicated by the observation that in three instances of aortic insufficiency, two of syphilitic and one of rheumatic origin, a similar volume contour was not obtained. However, during the course of these investigations we have observed the typical blunting and flattening of the volume pulse in lesions other than patent ductus. These included two cases of arteriovenous and one case of arteriosclerotic aortic aneurysm. (Fig. 5.) The similarity of the tracings in patent ductus and arteriovenous aneurysm is readily understood. The identity of the pattern in the presence of a

large arterial aneurysm and in patent ductus may be explained on the assumption that both the shunt and the arterial sac, functioning as a surge tank, smooth out comparatively small, fast volume and pressure changes such as the dicrotic notch. The mechanism may be compared to that of an electromechanical equivalent of a by-pass condenser. This explanation would also account for the equiphasic systolic and diastolic limbs and the flattening of the apex. Changes in volume amplitude from moment to moment are accounted for by fluctuations in volume flow to the periphery induced by a variable diversion of blood through the shunt with each systole of the heart. A large arterial aneurysm behaving as a reservoir may produce similar fluctuations in the circulating blood volume per beat.

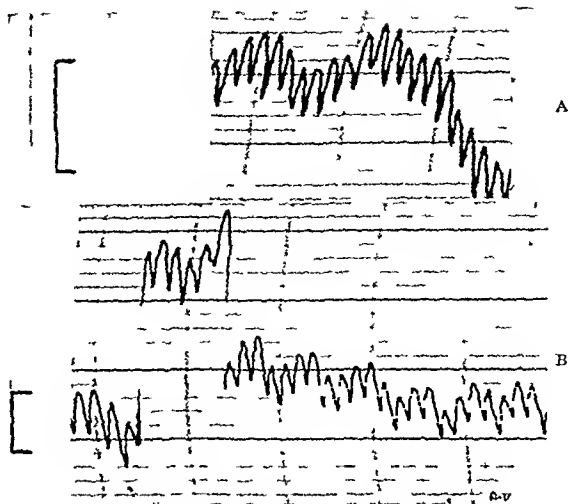


FIG 5 A, plethysmogram from the great toe of a patient with an arteriovenous aneurysm B, plethysmogram from the great toe of a patient with an arteriosclerotic aortic aneurysm Note the similarity of these tracings and those noted in instances of patent ductus

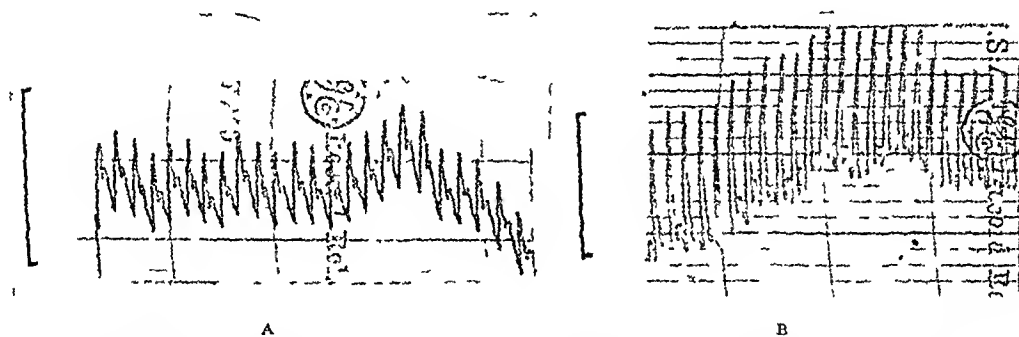


FIG 6 Plethysmograms from the finger of a normal subject before and after the administration of $\frac{1}{100}$ gr nitroglycerin A, the control Note the marked increase in volume pulse amplitude and the sharp decline in the position of the dicrotic notch following nitroglycerin.

Absence of similar plethysmographic alterations in the presence of free aortic insufficiency and in various intracardiac shunts is attributable to the fact that the major volume changes occur centrally within the chambers of the heart.

COARCTATION OF THE AORTA

The finger and toe plethysmograms normally differ. Although the two are essentially similar in contour, in the position of the dicrotic notch and in the slope of the component limbs, the amplitude of certain intrinsic volume deflections may differ sharply under normal conditions. Thus the uncorrected volume pulse and alpha waves are much larger in the great toe than in the

finger. The reverse is true of the respiratory waves. (Fig. 2.)

We have also observed that the sublingual administration of nitroglycerin produces characteristic alterations in the normal plethysmogram. These consist of a distinct increase in volume pulse amplitude, of a moderate increase in the amplitude of the alpha waves and in a pronounced descent in the position of the dicrotic notch on the diastolic limb. (Fig. 6.) Increases in amplitude are proportional in the finger and toe.

These variations in the normal and in the normal postnitroglycerin plethysmograms are diagnostically altered in the presence of coarctation of the aorta. When this condition is present, the amplitude of both the

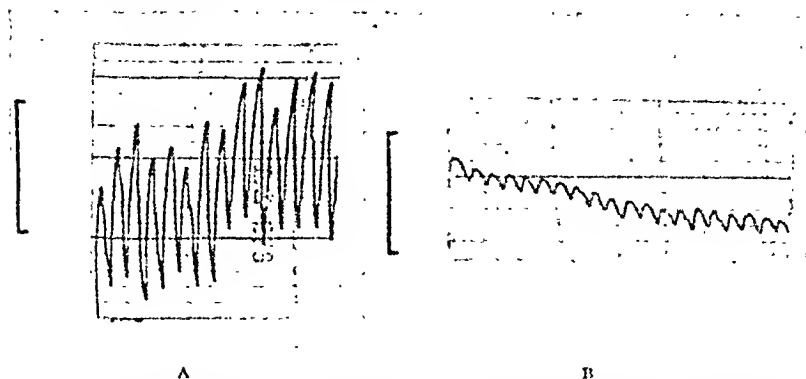


FIG. 7. Plethysmograms in a patient with coarctation of the aorta. A, tracings from the finger; B, tracing from the great toe. Note the pronounced reversal in volume amplitude relationships.

uncorrected volume pulse and the alpha waves in the toe never exceeds that in the finger. If the aorta is markedly constricted, the normal volume relationship may be reversed. (Fig. 7.) Thus the tracing from the toe may reveal a volume pulse of markedly diminished amplitude and an absence of alpha waves while the record from the fingertip shows well developed volume pulse deflections and alpha waves of large amplitude. Furthermore, the characteristic nitroglycerin effect may be manifest in the finger tracing while insignificant alterations appear in the toetip plethysmogram.

We have had the opportunity of analyzing the plethysmograms of six patients with suspected coarctation of the aorta because of diminished or absent femoral pulsations, or suggestive cardiac murmurs or radial pulse waves preceding the femoral pulse waves. Roentgen examination failed to reveal the characteristic notching of the ribs in any of these persons. Only two of the six patients presented classical hypertension in the upper and hypotension in the lower extremities. In three patients arterial pressure levels were similar in the upper and lower extremities; in the remaining patient normal pressure relationships existed. Angiocardiograms were obtained in five of these six patients and the clinical impression was confirmed in each instance.

A plethysmographic diagnosis of coarctation was made in all patients either because of a reversal in volume relationships in the tracings obtained from the finger and toe,

or the aforementioned variation in the response to nitroglycerin or the fact that the uncorrected volume pulse amplitude and alpha waves in the toe did not exceed those in the finger. In general, the plethysmogram, angiocardiograms and the additional clinical findings were comparable. When a pronounced degree of coarctation was demonstrated in the angiocardiogram, the plethysmogram showed pronounced reversal in volume relationships. This is exemplified in Figure 7 and was obtained in one of the patients who had hypertension in the upper extremities.

The angiocardiogram and the plethysmogram yield complementary rather than identical information. This is evidenced by the findings in two of the six patients in whom a significant degree of coarctation was demonstrable on the angiocardiograms. The plethysmograms, however, revealed volume pulse amplitudes in the toe either equal to or slightly smaller than those obtained from the finger. Such instances presumably indicate the existence of a fairly adequate collateral circulation. Thus the correlation of angiocardiographic and plethysmographic findings can be expected to aid in defining the indications for surgical treatment in cases of coarctation.

Application of microplethysmography to clinical medicine is as yet in its infancy. The technic offers a fruitful field for investigation, and it is as much the purpose of this report to encourage investigations by other groups as to present our own results. We

have used the microplethysmograph in various other disorders of the cardiovascular system and additional results are soon to be published. Our investigations in the problem of congenital heart disease are continuing.

We believe we are justified in stating that the microplethysmogram has been a valuable aid in diagnosis of patent ductus arteriosus and coarctation of the aorta. It should be part of the preoperative diagnostic survey, as much as physical examination and electrocardiography. Ease of recording and interpretation make the method especially valuable in those patients in whom typical signs are not present, or in whom such factors as age, sensitivity to diodrast or absence of necessary equipment make angiocardiology and cardiac catheterization inadvisable or impossible.

SUMMARY AND CONCLUSIONS

1. Microplethysmography has been applied to the study of congenital heart disease. Present investigations have dealt with patent ductus arteriosus and coarctation of the aorta.

2. Tracings of the finger and toetip volume pulsations were recorded and characteristic patterns were found.

3. In patent ductus the following alterations were found: the apex of each wave was blunt, broad, or flat; there was a loss of the normal difference between systolic rise and diastolic fall, the limbs tending to be equal; the dicrotic notch was either absent or barely discernible and tended to vary in position from beat to beat; small but significant fluctuations in contour and

volume amplitude appeared from moment to moment.

4. In coarctation of the aorta normal volume relationships in the finger and toe tracings were lost so that the volume amplitude and alpha waves in the fingertip tracing were greater than or at least equal to the analogous waves in the tracing from the toetip.

5. The findings illustrate the value of microplethysmography in diagnosis of these anomalies.

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Pheochromocytoma*

Report of a Case, with a New Diagnostic Test

VICTOR GUARNERI, M.D. and JAMES A. EVANS, M.D.

Boston, Massachusetts

THE first successful excision of a pheochromocytoma was reported by C. H. Mayo¹⁵ in 1927. Since then, there has been an increasing number of reports dealing with removal of this tumor. MacKeith,¹⁴ in an excellent review of the subject in 1944, stated that 165 cases of pheochromocytoma had been reported. Of these, thirty-six patients were operated on with ten fatalities. Since 1941, twenty-nine additional cases have been reported in English and American literature.^{2-6,8-14,16-20,22,24-26} Eighteen patients underwent operation and two deaths occurred.^{18,25} It is the purpose of this paper to describe an additional case of chromaffinoma of the adrenal gland, diagnosed preoperatively and successfully removed, in which a new diagnostic test was employed.

CASE REPORT

A twenty-three year old white, unmarried woman was first seen at the Clinic in February, 1946 complaining of attacks of weak spells. Cholecystectomy, appendectomy and dental extraction had been performed to relieve her present complaints but without avail. The patient stated that she had been in fairly good health until three years before admission when she noted onset of five or six daily attacks of weakness which would last five to ten minutes. These attacks came on suddenly without warning and at times awakened her from a sound sleep. The attacks were described by the patients as follows: "Suddenly there occurs a feeling that all the blood is draining out of my body, and I feel weak. There is an aching in my legs and a burning sensation in the pit of my stomach. Then I get a pain in my chest which goes down my arms, shortness of breath, and

palpitation of the heart. Next there is dizziness and a ringing in the ears followed by a severe throbbing headache and a pain in the back of the neck. Cold sweat breaks out in my hands and face and the hands become cold and blotchy while the sears on my body become purple. Then nausea and vomiting follow and the attack ceases but leaves me woozy and weak." Most of the attacks occurred after meals. Between attacks she felt perfectly well. Elsewhere she had been treated with a course of histamine by intravenous drip. It is interesting to note that in spite of the fact that histamine reproduced the symptoms the diagnosis was overlooked.

The patient was well nourished but poorly developed. The general system review for other symptoms was negative. Skull, pupillary reactions and ocular muscles were normal. Ophthalmoscopic examination revealed normal fundi. Lungs and heart were normal; apical and radial rates were 100 with regular rhythm. Blood pressure in the right arm was 102 mm. systolic and 94 mm. diastolic, in the left arm 106 mm. systolic and 84 mm. diastolic. No other physical findings pertinent to her present illness were discovered.

Tests of the urine were negative except for a trace of albumin. Hemoglobin was 13.6 Gm., red cell count 5,050,000 and white cell count 11,350. The differential count revealed 80 per cent polymorphonuclear cells and 20 per cent lymphocytes. Sedimentation rate was 22 mm. per hour; the Hinton test was negative. The fasting blood sugar was 100 mg. per 100 cc. During separate attacks of weakness the blood sugar was 147, 156 and 166 mg. per 100 cc., respectively. Serum calcium determination was 9.8 mg. per 100 cc., serum phosphorus 3.4 mg. per 100 cc., alkaline serum phosphatase 5.0 Bodansky units, acid phosphatase 0.4 units. Serum potassium during an attack was 21.3 mg. per 100 cc. (normal 18 to 22 mg. per 100 cc.).

* From The Department of Internal Medicine, The Lahey Clinic, Boston, Mass.

Gastric analysis showed free hydrochloric acid of 10 and total acid of 30. Basal metabolic rate was 9 per cent before and +36 per cent during an induced attack.

An electrocardiogram before an induced attack showed a rate of 100, high P_2 and flat T_3 .

from five to ten minutes. We were not able to induce attacks by abdominal massage, hyperventilation, epinephrine, nitroglycerine, changes in position or by the cold pressor test.

Operation was performed on the twenty-fifth hospital day by Dr. Richard B. Cattell. She

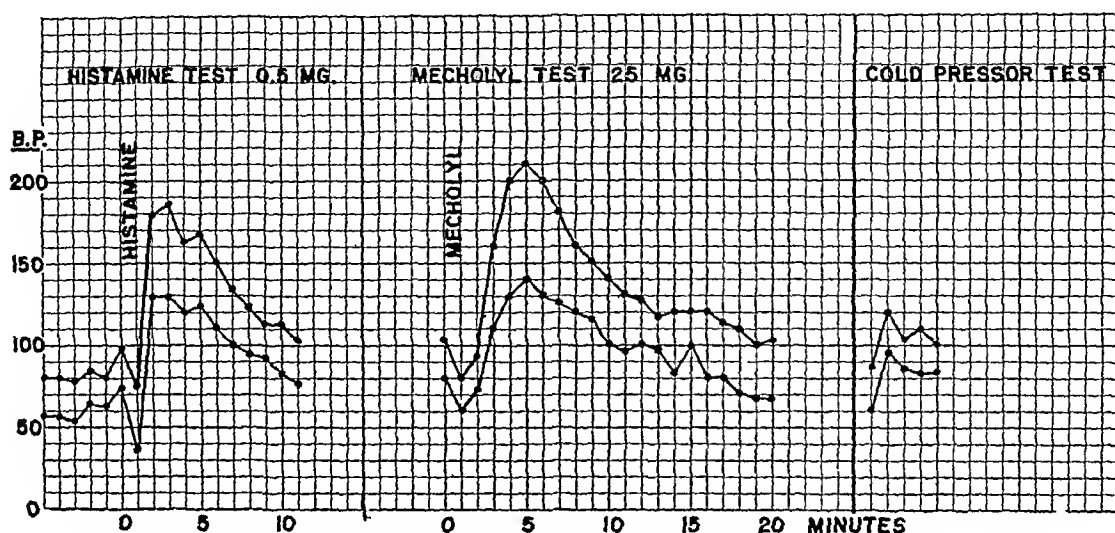


FIG. 1. Preoperative histamine, mecholyl and cold pressor tests in a case of pheochromocytoma.

During an induced attack the rate was 120 and T_3 became inverted. An electro-encephalogram was interpreted by Dr. Milton Greenblatt as showing a definitely atypical record consistent with a mild form of epileptic dysrhythmia, with no localized abnormality.

Roentgenologic examination after a barium enema showed the splenic flexure high under an elevated left diaphragm. Roentgenogram of the skull showed no localized changes and a normal sella turcica. Intravenous pyelography revealed the left kidney to be flattened superiorly so that the major superior calyx was at right angles to the pelvis. The depressed left kidney and elevated left diaphragm were considered to be consistent with a space-filling lesion in the left upper quadrant.

While the patient was at rest in the hospital, blood pressure ranged between 80 and 110 mm. systolic and 60 to 80 mm. diastolic. The patient had many spontaneous attacks, during one of which the blood pressure level rose as high as 230 mm. systolic and 140 mm. diastolic. We were able to induce attacks with 0.5 mg. of histamine intravenously and 25 mg. of mecholyl subcutaneously. With histamine, blood pressure rose from 80 to 185 mm. systolic and from 62 to 130 mm. diastolic; with mecholyl, from 104 to 210 mm. systolic and from 80 to 140 mm. diastolic (Fig. 1). The spontaneous attacks lasted

was prepared as follows: 10 mg. of desoxycorticosterone acetate was administered intramuscularly daily for five days before operation. Adrenocortical extract, 25 cc. intramuscularly and 25 cc. in 1,000 cc. of 5 per cent glucose and physiologic saline solution, was given the night before and immediately before operation. Whole blood, 500 cc., was also given during the surgical procedure.

At operation the right adrenal gland was explored first and found to be normal. During exploration blood pressure rose to 190 mm. systolic and 132 mm. diastolic. Through a left lumbar incision the tumor mass was readily exposed but it was necessary to resect a portion of the twelfth rib in order to remove the tumor mass. In doing so the pleura was accidentally nicked and respiratory distress developed. This was remedied by closing the tear after decompression of the pleural cavity and expansion of the lung by positive pressure. The tumor was found to be above and compressing the superior pole of the kidney but was not adherent to it. During manipulation of the tumor the blood pressure rose to 260 mm. systolic and 185 mm. diastolic and just before the pedicle was clamped pulmonary edema developed. The blood pressure was unobtainable. In retrospect, this was thought to be caused by extreme vasoconstriction with conse-

quent left ventricular failure accompanied by pulmonary edema, all of which led to a precipitate drop in blood pressure as measured in the brachial artery. The pedicle was immediately clamped and a transfusion of whole blood was started. Epinephrine, 0.5 cc., was given intramuscularly and 0.2 cc. intravenously.

operation. The blood pressure at this time was 110 mm. systolic and 70 mm. diastolic when she was lying down, 100 systolic and 70 diastolic sitting and 80 systolic and 70 diastolic when standing. Albumin had disappeared from the urine.

On pathologic examination by Dr. Shields

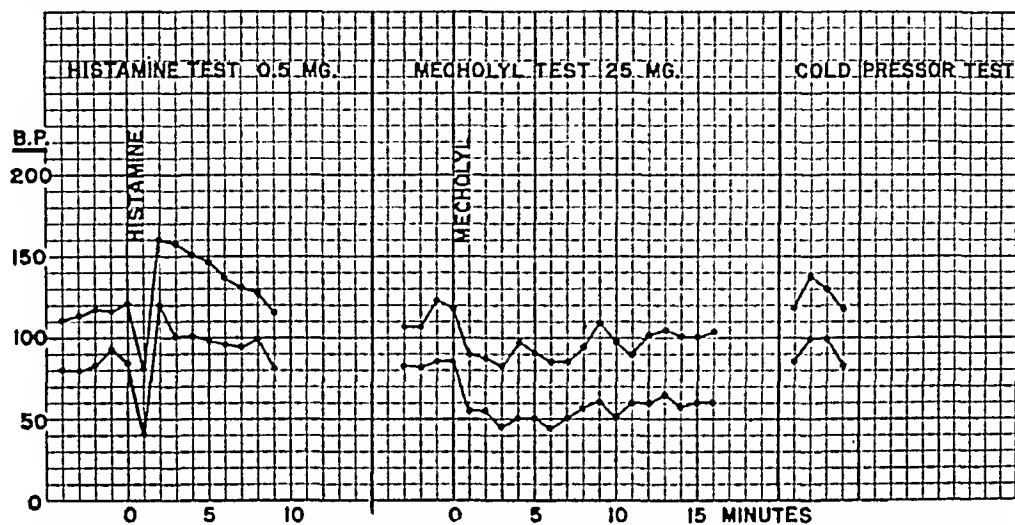


FIG. 2. Postoperative histamine, mecholyl and cold pressor tests in a case of pheochromocytoma. Note that the patient still reacts to histamine (hyper-reactor) but does not react to mecholyl after operation.

The blood pressure remained unobtainable for one-half hour after which it rose to 80 mm. systolic and 40 mm. diastolic. The tumor was quickly removed, one-half the left adrenal gland was left intact and the incision was closed. The patient was given oxygen by mask until most of the signs of pulmonary edema disappeared. She was then returned to her room; the blood pressure was 80 mm. systolic and 40 mm. diastolic. The anesthesia used was ether, later supplemented by cyclopropane.

Postoperatively, the patient had a relatively uneventful course except for the development of patchy atelectasis at the base of the left lung and a low grade temperature for several days. This was treated with penicillin. The postoperative blood pressure ranged from 84 to 126 mm. systolic and from 30 to 98 mm. diastolic, becoming stabilized to normal levels on the second postoperative day. Intravenous fluids were also administered routinely after operation. She was discharged on the seventeenth postoperative day. The mecholyl test repeated prior to discharge was normal; however, there was still a hyper-reactive response to histamine, 0.5 mg. intravenously. (Fig. 2.)

When seen again two months after discharge, the patient felt perfectly well, had gained some weight and had had no further attacks since

Warren, the specimen was found to be an encapsulated mass, 8 cm. in diameter, weighing 260 Gm. The mass had a smooth, glistening capsule with injected vessels running over the surface. The cut surface showed practically the entire mass to be occupied by a soft, bright red, jelly-like material, except for an irregular, yellow, encompassing border. Microscopically, none of the architecture of the adrenal gland remained. The entire mass was composed of cells which were apposed to each other in clusters and separated by fine strands of connective tissue in which numerous capillaries coursed. These clusters formed broad sheets punctuated by arterioles and dilated, congested vessels. The individual cells varied in size from about 15 to 45 μ , averaging about 25 μ ; they were sometimes oval or round but more often polygonal. The cytoplasm was acidophilic, slightly granular and contained vacuoles. The nuclei were oval, occasionally round, vesicular and measured about 10 to 20 μ in diameter; they were centrally or slightly eccentrically placed; rare nuclei were hyperchromatic but there were no mitoses and no multinucleated cells. Some portions of the tumor were covered by a thick capsule and there was invasion into this fibrous covering. Microscopic diagnosis was pheochromocytoma.

COMMENTS

Symptomatology, pathology and other general features of chromaffin tumors have been discussed elsewhere^{14,23} and need not be repeated. Our remarks will be confined to a description of the effects of certain drugs on a patient with pheochromocytoma. These observations have been utilized to construct a diagnostic test for the presence of this tumor.

The high surgical mortality rate of 28 per cent reported by MacKeith¹⁴ has generally been attributed to the shock effect of sudden withdrawal of epinephrine following excessive rise of blood pressure during the operation resulting from manipulation of the chromaffin tumor. It occurred to Dr. Elmer C. Bartels, of our medical staff, that an excess of anti-epinephrine factor (acetylcholine), predominant after removal of the tumor, might be responsible for the shock so often experienced immediately after excision of the tumor. He suggested, therefore, that mecholyl be given our patient preoperatively, reasoning that if an excess of acetylcholine was present, the patient should show none of the usual depressive effects from what would be to her a comparatively small addition of acetylcholine. Mecholyl (acetyl β methylcholine), 25 mg., therefore, was administered subcutaneously. The patient, however, exhibited the usual fall in blood pressure and then, to our surprise, within two minutes the blood pressure rose to 210 mm. systolic and 140 mm. diastolic. (Fig. 1.) A smaller dose of mecholyl (15 mg.) produced a similar response as did administration of an additional 10 mg. at the peak of the blood pressure elevation following the 15 mg. dose. It was apparent from these observations that there was no anti-epinephrine protection from excess acetylcholine and furthermore that mecholyl could not be used during the operation to protect the patient from paroxysmal hypertension during manipulation of the tumor. It could be reasoned also that atropine, the antidote for acetylcholine, could not be used to protect the patient from the partial collapse of blood pressure that usually

occurs immediately after removal of a chromaffin tumor.

In order to determine the reason for this unusual response to mecholyl the patient was given atropine before administration of this substance. (Fig. 3.) Atropine has no

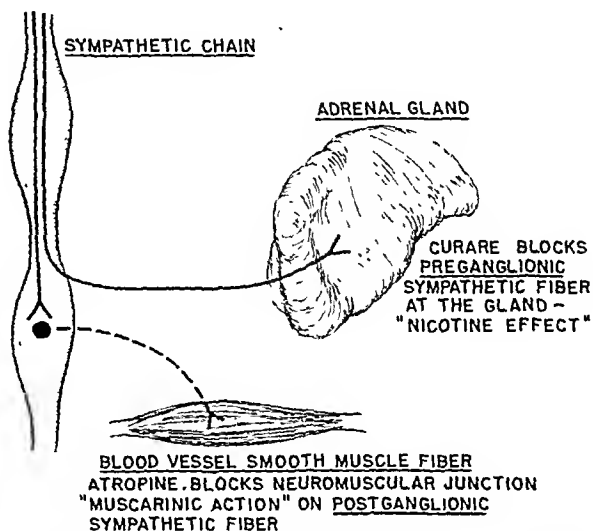


FIG. 3. Diagrammatic representation of "nicotinic effect" and "muscarinic action."

effect on autonomic ganglia.⁷ Its action is limited to blockage of the "muscarinic" or peripheral effects of parasympathetic activity, the postganglionic response. If the mecholyl response were a manifestation of muscarinic activity only, it should be blocked by atropine. If it were due to ganglionic stimulation, atropine should have no effect. Atropine, $\frac{1}{75}$ gr., was given subcutaneously after the resting blood pressure became stabilized. Five minutes later 25 mg. of mecholyl was given subcutaneously. No initial fall in blood pressure was observed, but within two minutes the blood pressure had risen to 230 mm. systolic and 190 mm. diastolic as in the original experiment without atropine. The various muscarinic side reactions of mecholyl, however, failed to occur. Approximately three hours later another 25 mg. of mecholyl was given. This time a slight fall of 10 mm. of mercury in pressure was recorded followed by a prompt rise. Again, none of the side reactions of mecholyl were present. These results would seem to indicate that the hypertensive effect of mecholyl in this patient was not the result of any peripheral

muscarinic action since the manifestations of such action, including the initial fall in blood pressure presumably due to vasodilatation, could be blocked by atropine.

The adrenal gland is innervated by preganglionic cholinergic fibers and is functionally equivalent to an autonomic ganglion. Theoretically, mechohyl could have elevated the blood pressure by a direct stimulating action on the synapse between the preganglionic fiber and the adrenal gland and its tumor. If this were true, it should have been possible to prevent the response by use of a drug which blocks transmission of impulses across the preganglionic synapse. Nicotine would have been the ideal drug to use for this purpose; unfortunately it was not readily available. Instead, we used curare, which is an autonomic inhibitor⁷ less potent, however, than nicotine.¹⁴ The patient was given 5 cc. of curare (intocostrin) intravenously. Within a few minutes, muscle and respiratory paralysis developed. While respiration was being maintained by positive pressure oxygen administration, 25 mg. of mechohyl was given subcutaneously. The typical mechohyl response occurred, first an initial fall in blood pressure followed by a rise in two minutes to 218 mm. systolic and 132 mm. diastolic. Inhibition of the preganglionic synapse failed to prevent the mechohyl-induced hypertension, suggesting either that mechohyl does not directly stimulate the synapse or that curare failed to block transmission across the synapse.

Mechohyl (acetyl β methyleholine), in contradistinction to acetylcholine, has principally a muscarinic action.⁷ It also has a nicotinic or ganglionic action⁷ but this is minimal. In atropinized animals it is usually impossible to produce elevation of blood pressure with mechohyl.⁷ In normal human beings response to mechohyl is a fall in the blood pressure level. The mechanism of mechohyl hypertension in pheochromocytoma is not entirely clear. Several possibilities exist: (1) The preliminary fall in blood pressure due to vasodilatation may act as a stimulus to compensatory sympathetic activity. In the presence of a

chromaffin tumor, a large reservoir of sympathomimetic substance, there may be an exaggeration of the compensatory response with resultant hypertension. Since response could be elicited in spite of elimination of the hypotensive stage by atropine, however, this explanation would appear invalid. (2) The ganglionic (nicotinic) action of mechohyl, even though slight, may be sufficient to produce hypertension when the effector structure is as potent as is pheochromocytoma. Militating against this is the fact that curare failed to block the mechohyl response. It is difficult to determine whether or not the dose of curare was sufficient to block completely the preganglionic synapse. (3) Since the curare effect was potent enough to suspend respiration, it would seem likely that the dose would have been enough to paralyze the preganglionic sympathetic-adrenal synapse. If this were true, then the hypertensive response to mechohyl in this patient could have been the result of the direct action of mechohyl on the chromaffin tumor itself. This appears to us the most probable interpretation.

Roth and Kvale²² administered 1 to 2 mg. of mechohyl by intravenous drip over a fifteen-minute period to a patient with a pheochromocytoma and failed to reproduce the typical paroxysmal hypertension. In view of our findings we believe that the method of administration was too slow and the dose too small to elicit response. The unique hypertensive response produced by mechohyl in our patient with a pheochromocytoma suggests use of the drug as a diagnostic test.

MECHOLYL TEST

The mechohyl test consists of administration of 25 mg. of the drug subcutaneously following a period of rest to obtain stabilized blood pressure and pulse rate. The blood pressure and pulse rate are recorded, after mechohyl is given, at one-minute intervals until they return to normal in fifteen to thirty minutes. A positive test is shown by a marked rise in the systolic and diastolic pressures. In this case there was a rise of

106 mm. systolic and 60 mm. diastolic above the resting levels following a preliminary fall lasting about one minute. The pressure returned to normal in fifteen minutes. Associated with the rise in blood pressure were all the symptoms character-

patients experienced sweating, salivation, tearing, dyspnea, flushing and a sensation of warmth, nausea, urge to defecate or urinate and an occasional headache. These subsided with return of the blood pressure to normal. In two hypertensive individuals

TABLE I
VARIATIONS IN BLOOD PRESSURE FOR VARIOUS TESTS*

Case	Histamine Test				Mecholyl Test				Cold Pressor Test			
	Blood Pressure		Difference in Pressure		Blood Pressure		Difference in Pressure		Blood Pressure		Difference in Pressure	
	At Rest	During Test	Sys-tolic	Dias-tolic	At Rest	During Test	Sys-tolic	Dias-tolic	At Rest	During Test	Sys-tolic	Dias-tolic
21	154/96	180/110	+26	+14	156/80	116/20	-40	-60	156/90	158/96	+2	+6
26	158/106	192/98	+34	-8	124/86	130/40	+6	-46	122/84	126/90	+4	+6
19	124/74	156/100	+32	+26	126/76	124/40	-2	-36	130/74	136/90	+6	+16
22†	130/80	188/140	+58	+60	116/76	100/60	-16	-16	124/78	130/92	+6	+14
27	120/70	164/84	+44	+14	130/78	80/48	-50	-30	140/76	166/90	+26	+14
		166/80	+46	+10								

* Tests were performed on five patients considered to be histamine hyper-reactors, two hypertensives and three normotensives. Note the rise in both systolic and diastolic pressures is greater after histamine than during cold pressor test in both hypertensive and normotensive subjects.

† Received 0.5 mg. of histamine instead of 0.05 mg.

istic of a paroxysmal attack of hypertension due to pheochromocytoma. In addition, the patient experienced the side reactions of mecholyl, which include nausea, salivation, epiphora, sweating and dyspnea.

In order to obtain information regarding the specificity of the test, it was performed on twenty-seven additional patients, ages twenty to sixty. Seven were normal and twenty had hypertensive vascular disease. Of the latter group eighteen had essential hypertension. Two had chronic glomerulonephritis with hypertension. In twenty-two the cold pressor test was also done and in nine the histamine test, described by Roth and Kvale,^{21,22} was performed.

The results in these twenty-seven controls were as follows: (1) With one exception, the twenty-seven patients showed an identical response to mecholyl; an immediate initial fall of systolic and diastolic pressures followed by a gradual return to normal levels in fifteen to thirty minutes. Almost all of the

the test had to be terminated with atropine at the end of ten minutes. One who complained of fainting spells developed a convulsive seizure associated with a marked fall in blood pressure; the other complained of severe substernal pain during the test. In one patient the systolic blood pressure rose 6 mm. of mercury over normal without a preliminary fall. The diastolic pressure, however, fell initially and never rose above the resting level. (2) Of the twenty-two patients on whom the cold pressor test was performed, seventeen showed a normal response consisting of a transient slight elevation of blood pressure less than 20 mm. Five showed a rise of more than 20 mm. and may be considered as hyper-reactors. These five, however, had perfectly normal mecholyl tests. (3) Of the group of nine patients on whom the histamine test was done, five had a rise in blood pressure of 20 mm. or more and are considered as hyper-reactors to histamine. Results of this

group are shown in Table 1. These five patients had normal mecholyl tests. Figure 4 shows graphically a typical mecholyl response in one of these patients. One patient in the histamine group in whom a diagnosis was made of "anxiety state," was given

test in this patient showed no rise of blood pressure after the usual fall and there were no symptoms suggestive of paroxysmal hypertension. In these four patients, especially the last one described, there appears to be a suggestive test for pheochromocytoma.

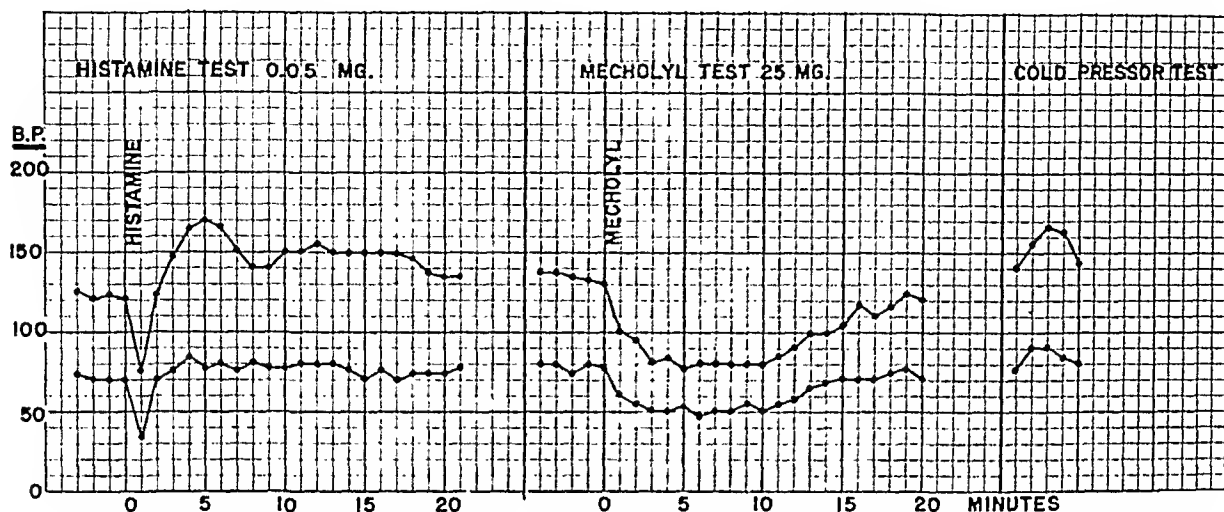


FIG. 4. Histamine hyper-reactor and normal mecholyl test. The chart also shows a typical normal mecholyl curve.

0.5 mg. of histamine instead of 0.05 mg. He showed a fall in blood pressure from 130 to 60 mm. systolic and from 80 to 0 mm. diastolic, followed by a prompt rise to 188 mm. systolic and 140 mm. diastolic, with a return to normal in forty-five minutes. This would appear to be a positive histamine test for pheochromocytoma. In view of the absence of other findings suggestive of pheochromocytoma, however, surgical exploration was not deemed justified. Both the mecholyl and cold pressor tests were normal. The cause for the rise in blood pressure in this patient is not definitely known. Unfortunately the test was not repeated using the usual 0.05 mg. dose of histamine.

Roth and Kvale reported that their patients had a smaller rise of blood pressure to histamine than to the cold pressor test. We found that four histamine reactors (two of these were hypertensive, two normotensive) did the opposite (Table 1), that is, when the same dose of histamine was given as Roth and Kvale used, the blood pressure level rose an average of 34 mm. systolic and 11.5 mm. diastolic. One of these four patients had the significant rise of 46 mm. systolic and 14 mm. diastolic. The mecholyl

cytoma although not the striking rise of 100 mm. systolic described in pheochromocytoma by Roth and Kvale. Since in no case except the patient with the pheochromocytoma did mecholyl produce a rise in both systolic and diastolic pressures, we suggest that the mecholyl test may be more specific than the histamine test in diagnosis of this type of neoplasm. We realize that definite conclusions cannot be drawn from so limited experience as is described here. Nevertheless, the results suggest the need for further trial of mecholyl as an aid in diagnosis of pheochromocytoma.

Recently, an adrenal tumor was found in a patient with grade 3 hypertension. The mecholyl test had been negative for pheochromocytoma. On microscopic examination of this tumor a report was made of carcinoma in an adenoma of the adrenal cortex.

SUMMARY AND CONCLUSIONS

A case of pheochromocytoma is presented.

The pharmacologic effects of mecholyl, atropine and curare in this patient are described and discussed. Mecholyl produced an initial transitory fall in blood pressure followed by a marked rise to hypertensive

levels. Atropine abolished the muscarinic reactions of mecholyl but failed to influence the rise in pressure. Curare did not affect the response to mecholyl in any way.

A diagnostic test for pheochromocytoma, based on the reaction to 25 mg. of mecholyl given subcutaneously, is described. An initial fall in blood pressure of short duration which is followed by a marked and more sustained rise to hypertensive levels constitutes a positive test. Of twenty-seven control patients receiving mecholyl, none showed this hyper-reactor response.

Comparison between the histamine and mecholyl tests is made. In a group of nine patients, five showed a hyper-reactor response to histamine. It is suggested that the mecholyl test may be more reliable than the histamine test in diagnosis of pheochromocytoma inasmuch as no hyper-reactors were noted among the controls when mecholyl was administered.

From the pharmacologic evidence presented it is deduced that mecholyl directly stimulates the chromaffin tissue of pheochromocytoma.

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Absorption and Metabolism of Lipiodol after Oral Administration*

Method for the Study of Fat Absorption and Fat Metabolism in Man

J. GROEN, M.D.

Amsterdam, Holland

ABSORPTION of fat in the small intestine is usually estimated either by microscopic examination of the feces or by determination of the fat content of the dried stools. Some investigators prescribe a diet of known composition during the test. The method has been improved by Van Hees¹ but is still not satisfactory. The main objection is that it is impossible by this method to distinguish between exogenous fat, the lipoids that occur normally in the stools, and fatty acids of low molecular weight that are formed inside the intestine from other compounds.

Van Creveld² has used iodized fat, iodipine, for the study of fat absorption. After oral administration of this substance he made qualitative tests for the presence of inorganic iodine in the urine. Trémolières and Cheramy³ determined the iodine excretion in the urine of the first twenty-four hours after ingestion of lipiodol as a measure of fat digestion. Pansdorf⁴ followed by roentgenograms the disappearance of an emulsion of iodipine which had been introduced through a duodenal tube. In 1936 Formijne⁵ used iodized fatty acids to study their transport from the small intestine into the mesenteric lymphatics. Kuster⁶ used iodipine to demonstrate that the intestine of infants absorbs emulsified fats better than fats in a non-emulsified condition.

For the present investigation we used Lipiodol Lafay, a heavy liquid preparation of iodized poppy-seed oil. In this preparation the iodine is in firm chemical com-

bination as evidenced by the negative results of all tests for inorganic iodine. Its high specific gravity (1.35) makes it possible by roentgen-studies to follow its passage into the stomach and small intestine after it has been administered by mouth. In normal people the lipiodol shadow gradually disappears as absorption of the fat proceeds. When fat absorption is impaired, a considerable part of the contrast medium remains visible in the x-ray films; it escapes absorption in the small intestine and may produce a contrast picture of the colon. This furnishes us with the possibility of a roentgenologic function test for estimating the efficacy of the absorption of fat. In addition, quantitative estimation of iodine appearing in the stools after administration of lipiodol is a chemical test for the absorption function of the intestine which can be carried out simultaneously. Finally, the amount of inorganic iodine which is excreted in the urine serves as a yardstick of the metabolism of lipiodol after its absorption, and through this we may gain insight into the metabolism of ingested fat.

METHOD

It is necessary to exclude from the test those patients who are hypersensitive to iodine. For this reason 0.5 Gm. of potassium iodide is administered to the patient on the evening before the test. Next morning the patient is seen and special attention is paid to rashes, colds, rhinitis, headache, conjunctivitis, etc. The test is carried out only if these symptoms are absent.

At 7:30 A.M. the patient receives a breakfast

* From the Department of Medicine of the Wilhelmina-Gasthuis, Amsterdam, Holland. With the technical assistance of Miss N. ten Bruggencate and Miss G. C. Mager.

consisting only of two biscuits and 300 cc. of tea. At the same time a mixture is given of 10 cc. Lipiodol Lafay (so-called "descending" lipiodol, said to contain 40 per cent iodine) and 10 cc. olive oil.

This quantity contains 4.2 Gm. of iodine.* Addition of olive oil is necessary as the undiluted lipiodol is of such heavy consistency that it is difficult to swallow. It would also remain too long inside the stomach. Between 7:30 and 12:00 no food is taken and during the test no drugs are given. In preliminary experiments x-ray studies of the intestinal tract were made at short intervals. It appeared that a satisfactory picture of the course of the absorption could be obtained by taking x-rays at two, three and one-half, five, eight and ten hours, respectively, after administration of the contrast medium.

All urine and feces are collected, including those of the night before the test, after potassium iodide has been given. In the beginning the iodine content of feces and urine was separately determined in twenty-four-hour samples. Later a single determination of the total excretion appeared to be sufficient. For this purpose the urine was stored in large bottles. After twelve days the total quantity was measured and the iodine content was determined in an aliquot sample. The feces were also collected, weighed, mixed by shaking in a special shaker by means of which a homogeneous mixture could be obtained, and the iodine determined in a weighed aliquot. The largest quantity of iodine is excreted during the first eight days after the test; after this only small quantities of iodine appear in the feces and urine. It was found that by terminating the collection of feces and urine after twelve days no error was made. In cases in which speed is required it is justifiable to terminate the collection of the excreta after eight days.

Determination of the iodine content was made by the method of Mathews.⁷ A weighed quantity of feces or urine is heated with chromic acid and sulfuric acid by which all iodine is oxidized to iodate. The oxidation flask is connected to a special distilling apparatus and the iodate is reduced by addition of phosphorous acid to hydriodic acid and free iodine. These are distilled and received in a solution of potas-

* According to the manufacturers, 10 cc. of lipiodol should contain 5.4 Gm. of iodine. However, in the samples of lipiodol used by us we found only 4.2 Gm. (The American product is standardized to meet U.S.P. requirements of 540 mg. iodine per cc.)

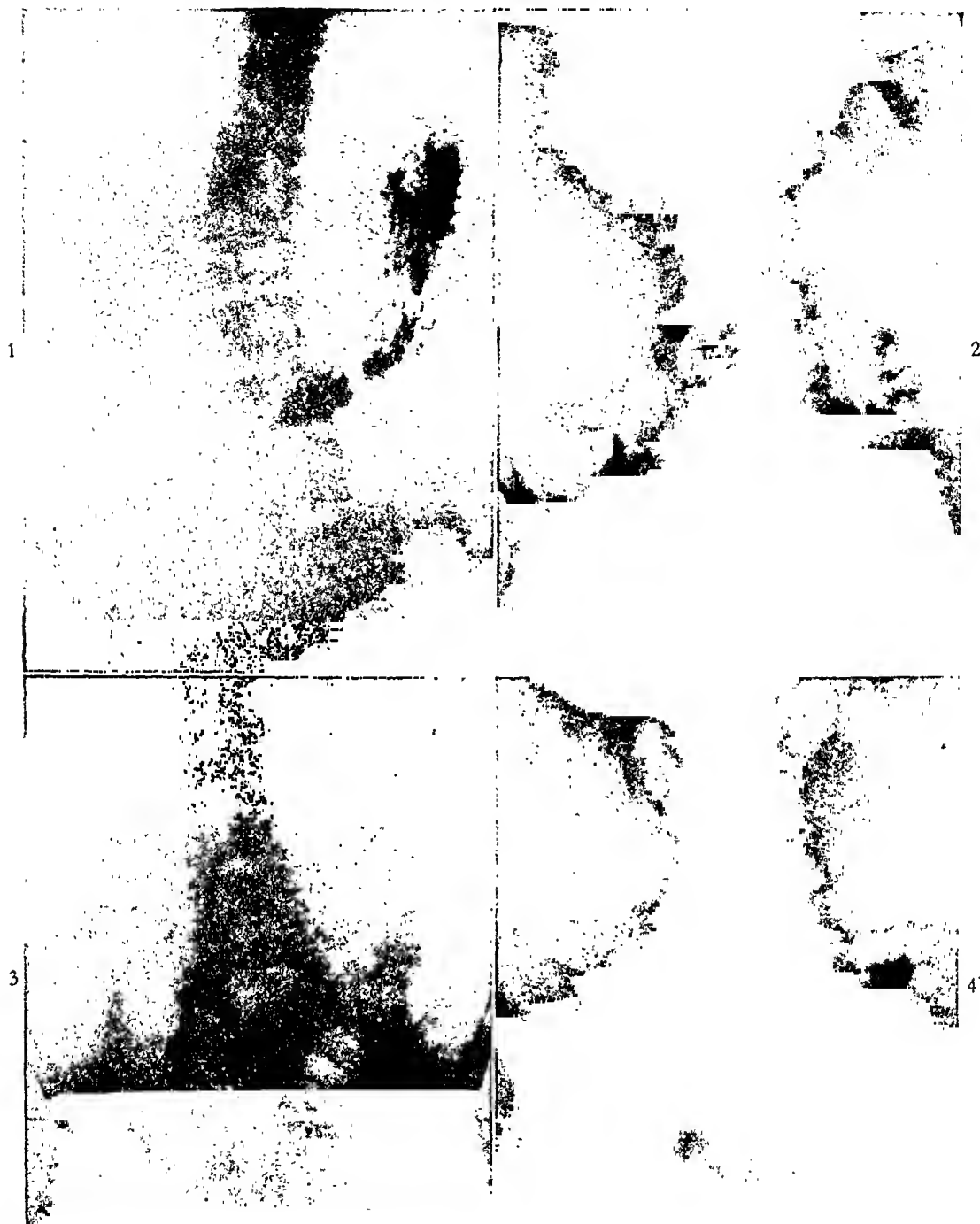
sium carbonate and sulfurous acid at which time they are transformed into potassium iodide. At the end of the distillation bromine is added. The excess of bromine is removed by boiling and the potassium iodate which has been formed is titrated with sodium thiosulfate after addition of potassium iodide and acetic acid. Inorganic iodide and lipiodol added to urine and stools were quantitatively recovered by this method.

RESULTS OF THE ROENTGENOLOGIC STUDIES

In Normals. Immediately after the lipiodol is swallowed the contrast medium is seen to form large drops along the mucous membrane of the stomach where they gradually merge into a relief picture of the mucous membrane.* (Figs. 1 to 4.)

After about one-half hour the lipiodol appears in the duodenum where it gives a distinct picture of the Kerckring's folds. Then the contrast medium enters the jejunum. In almost all subjects the stomach is nearly emptied after two hours and completely so after three and one-half hours. In the duodenum small amounts giving sharp contrast are still present after two hours. After two hours most of the lipiodol is found in the jejunum as small scattered flakes. (In some cases we found the lipiodol after two hours for the greater part in the ileum.) After three and one-half hours more than one-half of the oil is absorbed and much less lipiodol is visible in the x-ray picture than after two hours. At the same time the image appears less distinct owing to dilution and emulsification of the lipiodol. After five hours very little of the contrast medium is left. A little lipiodol may be present in the cecum. One of the characteristics of normal lipiodol absorption is that only a very small part of the contrast substance reaches the cecum. It is noticeable that the small residue present in the lower part of the ileum and in the cecum gives sharper contrast than in the former plates when the entire amount of lipiodol was in the small intestine. This is probably due to concen-

* This relief picture has not been further studied in the present investigation. It would be worth while to compare the "fat relief picture" of the stomach with that obtained after administration of a barium meal.



FIGS. 1 to 4. Progression of lipiodol through the intestinal canal immediately and two, five and eight hours, respectively, after its ingestion by mouth in a normal individual.

tration of the contrast medium in the lower part of the intestine by absorption of water. After eight hours the small intestine is completely empty. The few drops of lipiodol which have reached the large intestine are seen as small spots in the ascending colon

but the contrast is poor. After ten hours the x-ray shows a normal picture so that anyone examining the film without knowledge of the administration of a contrast medium would see nothing unusual except, after eight and ten hours, a shadow in the region



FIGS. 5 TO 8. Progression of lipiodol through the intestinal canal immediately and two, five and eight hours, respectively, after its ingestion by mouth in a case of non-tropical sprue.



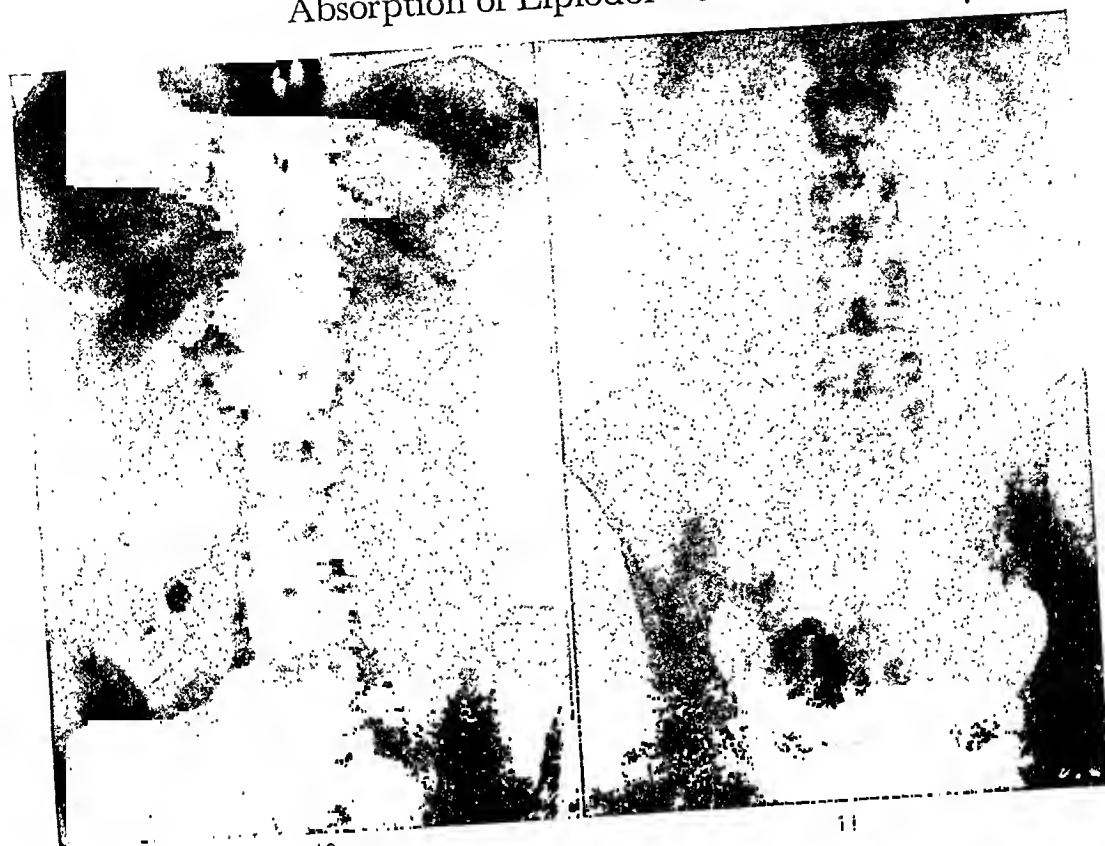
FIG. 9. Contrast picture of the colon ten hours after ingestion of lipiodol by mouth, indicating diminished absorption in a case of tropical sprue.

of the urinary bladder. This is due to the high specific gravity of the urine in which part of the lipiodol iodine is excreted as inorganic iodine.

In Patients with Various Pathologic Conditions. Normal results of the tests were obtained in various disease conditions. In two patients with anorexia nervosa with extreme emaciation the lipiodol picture was normal. In a third patient, in whom the diagnosis of pituitary cachexia was made, normal results of the lipiodol test proved that the extreme emaciation of this patient was not caused by diminished absorption of ingested fat. One patient with adiposity showed normal fat absorption. One subject with anorexia nervosa also had achylia gastrica. This apparently had no influence upon the absorption of lipiodol, which was normal. The same was observed in a patient with achylia gastrica with hypochromic anemia, in whom a normal lipiodol absorption also was found. Two patients with typical duodenal ulcer with high acid content of the stomach and one with uncomplicated cholelithiasis also had normal fat absorption.

Most interesting were the x-ray studies of the absorption of lipiodol in tropical and non-tropical sprue. We were able to examine six patients. In all cases an abnormal x-ray picture was obtained. The lipiodol left the stomach in the normal time. However, after two, three and one-half and five hours abnormally large quantities of lipiodol were still present in the small intestine. In all these patients the cecum filled with an abnormal amount of lipiodol which in some cases produced an excellent relief picture of the colon by the unabsorbed iodine-containing fat. (Figs. 5 to 9.) The disturbance in fat absorption was not equally pronounced in all patients. Two patients with non-tropical sprue were examined before and after treatment with a diet rich in protein and poor in fat and large doses of liver extract. In both cases the lipiodol test showed definite improvement after this therapy. In one case of tropical sprue the absorption even became completely normal after treatment.

Figures 10 to 12, the pictures of a patient with tuberculosis of the small intestine, show that after three and one-half to five hours large quantities of lipiodol were still present in the small intestine; after eight hours complete filling of the colon was obtained. Evidently in this case a large part of the lipiodol had escaped absorption in the small intestine. In contrast to this, in two patients with tuberculosis of the peritoneum (without diarrhea) normal lipiodol pictures were obtained. One patient with a gastrojejunocolic fistula (Figs. 13 to 15) was studied. Immediately after entering the stomach the lipiodol was seen to divide into two parts, one of which reached the small intestine via the gastroenterostomy opening; the other part almost immediately reached the descending colon from the stomach. Of the lipiodol passing through the small intestine, a smaller quantity than normal was absorbed. Evidently the disturbed fat absorption in cases of gastrojejunocolic fistula is caused not only by the fact that part of the food immediately reaches the colon, but also by disturbed absorption of



10

11



12

FIGS. 10 to 12. Progression of lipiodol through the intestinal canal two, five and eight hours, respectively, after its ingestion by mouth in a case of intestinal tuberculosis.



FIGS. 13 TO 15. Progression of lipiodol through the intestinal canal one-fourth, two and eight hours, respectively, after its ingestion by mouth in a case of gastrojejuno-colic fistula.

that part of the food which passes through the small intestine. A marked impairment of fat absorption was found in a patient with pancreatic insufficiency. This was a patient with a common duct stone. At operation the stone was found so firmly impacted in the papilla Vateri that it was decided to leave it there and to make a palliative anastomosis between the gall-bladder and the stomach. After operation the jaundice cleared but the patient was troubled with fatty stools. The disturbance in fat absorption is illustrated in Figures 16 to 18.

Three patients with ulcerative colitis were examined. In one, the disease was mild and of short duration. Here the lipiodol picture was almost normal. In two patients who had been suffering from the disease for a long time and who were in poor general condition, the roentgenologic picture after eight hours showed an excessive amount of unabsorbed lipiodol. This disturbed absorption of fat in patients with ulcerative colitis is of great importance. It is due to a disturbance of the ileum which can sometimes be verified by "routine" x-ray examination by means of a barium meal. Many patients with long-standing ulcerative colitis show an abnormal picture of the last loop of the ileum. It is important to keep this disturbed absorption in mind, especially in connection with the therapy of ulcerative colitis.

We examined four patients with pernicious anemia in relapse. In all, an impaired absorption was demonstrated roentgenologically. However, the impairment was not so pronounced as in those with sprue. These facts, together with earlier findings,⁸ make it probable that impaired absorption contributes toward development of deficiency in pernicious anemia.

CHEMICAL STUDIES

After administration of lipiodol, iodine is always found in the feces. This iodine seems to be present in organic form only, for when the feces are shaken with water we never found iodine after addition of nitric acid

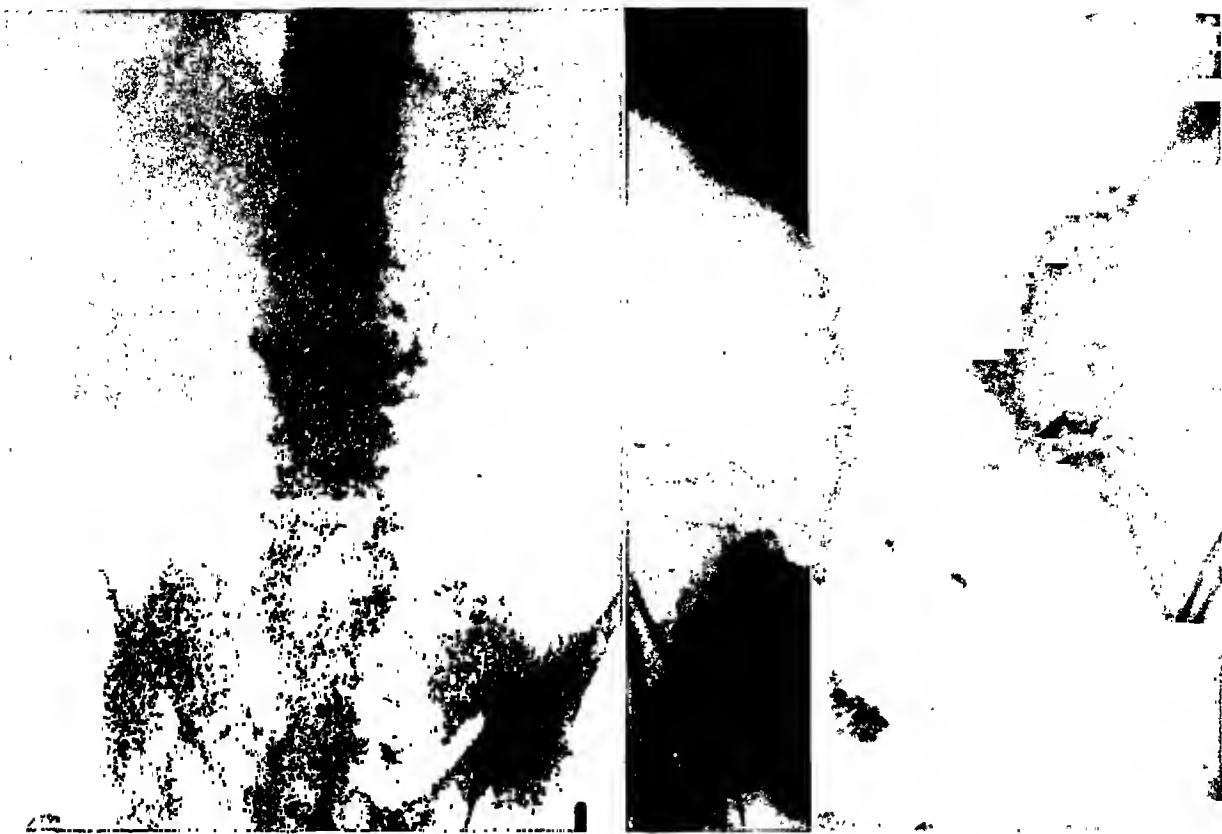
followed by addition of starch or extracting with chloroform. Also after incubation of lipiodol with gastric juice, duodenal juice or a feces suspension we never found free iodine. When the feces were dried and extracted with ether, 80 per cent of the iodine content passed into the ether. On shaking the feces emulsion with ether after acidifying with hydrochloric acid, all the iodine passed into the ether. Apparently non-absorbed lipiodol is present as neutral fat or as fatty acid to the extent of about 80 per cent and about 20 per cent as soaps. The urine always contains inorganic iodine after the test.

In our first investigations the iodine contents of the urine and feces were determined daily. The curve of the iodine excretion shows a definite course. During the first four to seven days the excretion in the urine and feces increased rapidly, after this the daily output diminished gradually. After eight to eleven days the excretion was usually reduced to a few mg. of iodine per day.⁹

The iodine administered as lipiodol was always 4.2 Gm.; on the evening before the test the patient received 0.5 Gm. of potassium iodide which contains 0.383 Gm. inorganic iodine. Control studies in normal individuals and in patients with sprue who received only 0.5 Gm. of potassium iodide without lipiodol revealed that this inorganic iodine is almost completely absorbed and excreted in the urine so that all the iodine found in the feces after the test may be considered to be derived from the lipiodol.

Results of the determinations of iodine in the stools are given in the first column of Table 1, expressed as percentages of the amount of iodine administered as lipiodol. The second column gives the percentage of lipiodol iodine absorbed (by subtraction). The third column indicates the percentage of iodine recovered from the urine.

Excretion with the Feces. After administration of 4.2 Gm. of lipiodol iodine, normal persons were found to excrete only 100 to 400 mg. of iodine with the feces, which



16

17



18

Figs. 16 to 18. Progression of lipiodol through the alimentary canal two, eight and twenty-four hours, respectively, after its ingestion by mouth in a case of pancreatic insufficiency.

means that in normal circumstances 2 to 9 per cent of lipiodol escapes absorption.

In sprue the quantities of lipiodol lost with the feces were much greater. In five patients with non-tropical sprue the iodine content of the feces varied between 807 mg.

with the well known fact that non-tropical sprue can be greatly improved but not completely cured by therapy.¹⁰ In one patient with tropical sprue who was examined after treatment normal absorption of the lipiodol was found.

TABLE I*

IODINE OUTPUT IN FECES AND URINE AFTER ORAL ADMINISTRATION OF LIPIODOL (4.2 GM. IODINE)

Name	Diagnosis	Iodine in Feces %	Iodine Absorbed %	Iodine in Urine %	Iodine Retention %	Remarks
K. K.	Normal	7.8	92.2	17.1	81	
Tc.	Normal	1.8	98.2	31.7	68	
Sn.	Normal	6.7	93.3	7.7	82	
G.	Normal	2.9	97.1	52.7	45	Losing weight
B.	Normal	8.5	91.5	37.7	59	On a reducing diet
R.	Sprue	77.2	22.8	4.6	85	
R.	After treatment	47.8	52.2	19.5	62	
v. d. S.	Sprue	36	64	24.8	61	
P.	Sprue	19.2	80.8	5.8	92	Mild case
W.	Sprue	45	55	9.6	82	
W.	After treatment	27.6	72.4	17.1	77	
N.	Sprue	31.2	68.8	4.3	93	
v. O.	Tropical sprue (after treatment)	1.6	98.4	62.4	37	
H.	Obstructive jaundice	33	67	1.4	98	Diet poor in fat
A.	Obstructive jaundice	39.5	60.5	5.9	92	Diet poor in fat
T.	Gastrojejunal fistula	51.6	48.4	20.9	58	
B.	Fistula of ileum	18.3	81.7	78.5	4	Losing weight
v. d. W.	Tuberculous peritonitis	6.6	93.4	48	48	
L.	Intestinal tuberculosis	36	64	26	59	
P.	Ulcerative colitis	15	85	53.7	36	Losing weight
B.	Ulcerative colitis	15.4	84.6	54	36	Losing weight
N.	Ulcerative colitis (proctitis)	6	94	28	71	
O.	Pernicious anemia	10	90	44.4	50	
S.	Pernicious anemia	3.1	96.9	20.6	78	
Sp.	Pernicious anemia	5	95	53	44	
H.	Pernicious anemia	12	88	63.4	28	
F.	Resected stomach	29.8	70.2	32.6	54	With pernicious anemia
B.	Resected stomach	5.7	94.3	40	57	
S.	Gastro-enterostomy	20.7	79.3	29	64	
v. K.	Castor oil	40.7	59.3	4.4	92	Gaining weight
H.	Paraffin liquid	45.5	54.4	30.7	87	Gaining weight
K.	Normacol	9	91	40.4	56	
G.	Cholelithiasis	9.2	90.8	53.3	42	
O.	Cholecystectomy	18.6	81.4	28	66	
S.	Paget's disease	1.5	98.5	45.7	54	
P.	Gaucher's disease	10.8	89.2	78.1	12	Losing weight

* The first three columns give the quantity of iodine as percentage of the ingested amount; the retention is given as percentage of the quantity that was actually absorbed.

(19.2 per cent) and 1,899 mg. (77.2 per cent). In two subjects with non-tropical sprue considerable improvement was obtained by treatment with diet and liver extract; however, the absorption did not become quite normal. This is in agreement

Severely disturbed absorption was found in patients with obstructive jaundice. We examined two patients with carcinoma of the papilla Vateri. Both showed a markedly increased excretion of iodine in the feces (1.660 and 1.387 Gm. respectively). In these

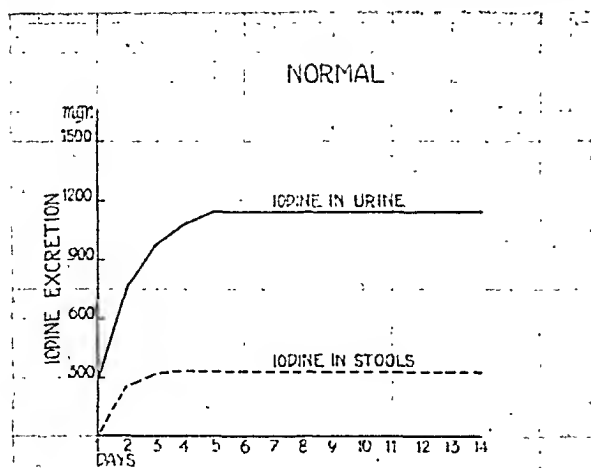


FIG. 19. Excretion of iodine in urine and stools after ingestion of lipiodol by mouth in a normal subject; iodine excretion in the urine exceeds the excretion in the stools.

cases, instead of 91 to 98 per cent, only 60 per cent and 67 per cent of the fat was absorbed.

The absorption of fat was also markedly disturbed in the patient with gastrojejuno-colic fistula and in a patient with surgical anastomosis of the ileum. One patient with tuberculosis of the peritoneum had a normal absorption whereas in a patient with intestinal tuberculosis a distinct disturbance was found. Two of four patients with pernicious anemia had a normal, two others an increased iodine content in the feces. One patient, who ten years previously had a resection of the stomach, was examined and found to have pernicious anemia. Examination with lipiodol proved that a disturbed fat absorption was present; the feces contained 1.253 Gm. of iodine, i.e., only 70 per cent had been absorbed. Another patient with a resected stomach had a normal fat absorption whereas a patient with a gastro-enterostomy had a disturbed excretion (20.7 per cent in the feces).

Three patients suffering from ulcerative colitis were examined, two of whom were severely ill. These two had disturbed absorption. In the other patient, in whom the disease was mild and restricted to the rectum, a normal absorption was found.

It appeared that lipiodol is not as well absorbed when given with a laxative. In one case we gave a normal test person the

lipiodol together with one tablespoonful of liquid paraffin. A second normal person received 150 cc. of 5 per cent magnesium sulfate solution and a third an agar preparation (normacol) simultaneously with the lipiodol. The first and second patient showed diminished fat absorption. This observation indicates that laxatives should not be given together with other medications or during meals as this may impair the absorption, especially of fat, fat-soluble vitamins and drugs.

Special attention must be given to the result in a patient with Paget's disease. In this patient we found the smallest iodine content of the feces which we have encountered so that excellent absorption was apparently present. In this connection it is noteworthy that Althausen¹¹ discovered rapid absorption of galactose in a patient with Paget's disease.

Excretion in the Urine. In normal individuals in whom the bulk of lipiodol is absorbed, excretion of iodine in the urine is much higher than in the feces. This situation is reversed in the severely disturbed absorption in cases of sprue. These patients excrete more iodine in the feces than in the urine. (Figs. 19 and 20.)

The amount of iodine excreted in the urine appeared to differ widely both in normal individuals and in the patients. The variation is due in the first place to a difference in absorption, but even after lipiodol has been absorbed its fate in the body differs in different individuals. Part of it is stored in the body, part of it is oxidized. It is only on oxidation that inorganic iodine is liberated from lipiodol. The amount of inorganic iodine which is set free, therefore, may furnish us with a yardstick to measure the amount of the oil which has been oxidized and by inference may give us an insight into the mechanism which determines the proportion of food fat which is oxidized compared with the amount which is stored.

Retention of Iodine. In the third column of Table I the percentages of retained iodine are given. They were calculated by sub-

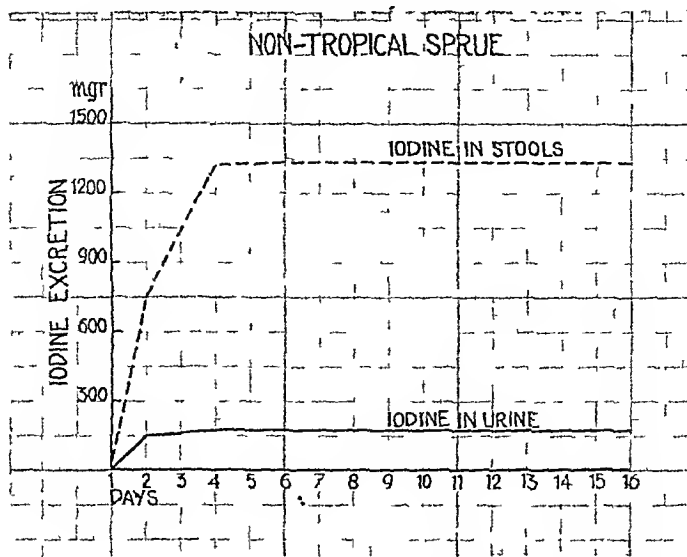


FIG. 20 Excretion of iodine in urine and stools after ingestion of lipiodol by mouth in a case of non-tropical sprue, iodine excretion in the stools exceeds the excretion in the urine.

tracting from the urinary iodine 0.383 Gm., the amount derived from the potassium iodide given the evening before the test. The figure thus obtained is expressed as a percentage of the amount of iodine absorbed from the lipiodol. It is assumed to indicate the percentage of lipiodol which has been oxidized. One hundred minus this figure is regarded as retained. As the body possesses only a limited capacity for storage of inorganic iodine it may be safely assumed that the percentage of iodine retained represents the percentage of ingested fat stored.

The number of patients examined under different circumstances has not been large enough to allow of definite conclusions about the various mechanisms that determine the relative proportion of ingested fat which is utilized and stored. First among the factors that appeared to influence the storage of fat is the caloric balance of the body. Normal persons and patients who at the time of the test were putting on weight exhibited marked retention of lipiodol. Individuals who were losing weight retained much less, among them a normal woman who followed a reducing diet while she was undergoing the test. A second factor appeared to be the relative proportion of fat in the diet. We found very great reten-

tion in the two patients with obstructive jaundice and in some of our patients with sprue, all of whom were on a diet that was particularly poor in fat.

CRITICAL APPRAISAL OF THE METHOD

Examination of the absorption of lipiodol by means of x-rays and the excretion of iodine in the feces is a useful method for the study of fat absorption. However, it cannot be denied that the method has its disadvantages. The apparatus is rather complicated, the test is rather expensive. The test cannot be carried out in patients who are hypersensitive to iodine. In severely ill patients the test cannot be performed. Furthermore, it is often difficult to evaluate the x-ray film in patients with slight disturbances in absorption. Moreover, it must be kept in mind that the absorption determined in this way is more the result of the collaborating functions of all digestive organs (emptying of the stomach, excretion of bile and pancreatic juice, digestive activity, velocity of passage through the intestine, passage through the intestinal villi, phosphorylation, etc.) than a function test of the isolated absorptive capacity of the intestinal canal.

In interpreting the results we must point to the fact that a disturbed fat absorption

need not be accompanied by diminished absorption of other food substances. Finally, it seems too early to judge the usefulness of the method for estimation of the tendency of the body metabolism towards fat utilization or storage.

SUMMARY

1. The author describes a method for study of the absorption of fat and of its subsequent metabolism. In the test the fate of an iodized oil (lipiodol) after oral administration is followed by: (1) The disappearance of the contrast shadow from x-ray films of the intestinal tract taken at regular intervals; (2) the determination of iodine excretion in the stools; (3) the determination of the amount of iodine excreted in the urine.

2. Normal absorption of lipiodol was found in achlorhydria, duodenal ulcer, uncomplicated cholelithiasis, tuberculosis of the peritoneum, obesity and anorexia nervosa.

3. Diminished fat absorption could be demonstrated in sprue, obstructive jaundice, intestinal tuberculosis, severe ulcerative colitis, gastrojejunal fistula, pancreatic insufficiency, in some cases of pernicious anemia and sometimes after stomach operations. The impaired absorption in non-tropical sprue improved but did not become completely normal after treatment with diet and liver extract. Administration

of laxatives with lipiodol had an unfavorable influence on absorption.

4. Excretion of iodine in the urine after administration of lipiodol by mouth is not a good measure of absorption. It may, however, give insight into the relation between the quantity of ingested fat which is oxidized and the amount which is stored under different circumstances.

Acknowledgment: The author is greatly indebted to the late Dr. A. Grunbaum for much valuable help and advice with the chemical part of the work.

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Reiter's Syndrome*

A Report on Four Patients Treated with Streptomycin

THOMAS A. WARTHIN, M.D.

West Roxbury, Massachusetts

THE original description of a syndrome occurring in young males characterized by urethritis, conjunctivitis and arthritis was made in 1916 by Reiter¹ in Germany. A number of reports followed in continental literature but it was not until twenty-six years later that Bauer and Engleman² first described similar cases in America. During the past two years an increasing number of cases have been recognized and reported in America²⁻¹³ and Great Britain.¹⁴⁻²¹ The clinical features of the syndrome have been well described in these papers. However, an analysis of these reports results in the conclusion that as yet a definite etiologic agent has not been determined, nor has a satisfactory treatment been found for this lengthy and often relapsing disease. In this communication four additional cases are reported because of the finding of pleuropneumonia-like organisms in the urine and joint fluid of one case and in the urine of a second case, because unusual myocardial changes were noted, and because of the suggestively promising results of the treatment of this disease with streptomycin.

CASE REPORTS

CASE I. R. F., a twenty-one year old ex-marine, entered the Veterans Administration Hospital, West Roxbury, Massachusetts, April 15, 1946, complaining of recurrent attacks of urethritis, conjunctivitis and arthritis of one year's duration. Two weeks after sexual exposure in Hawaii, in April 1945, he developed an acute urethritis. Smears were negative for gonococci and the urethral discharge was not affected by

treatment with sulfadiazine or penicillin. Approximately one week after the onset his eyes became inflamed, followed by the appearance of a swollen, painful right knee joint. Subsequently the left knee and right ankle were involved and he experienced considerable pyrexia. He was hospitalized for eight months and finally discharged from the Marines, March 5, 1946. On April 3, 1946, a purulent urethral discharge recurred with subsequent dysuria and urinary frequency. On April 5th both eyes became swollen and red. On April 8th his mouth became sore and superficial ulcerations were noted on the glans penis. On April 12th the right knee again became hot, swollen and painful, followed by the same condition in the left knee on the day of admission.

Examination revealed an acutely and chronically ill young male. His temperature was 102°F., pulse 124, respirations 22. The conjunctivae were deeply injected and the lids were crusted with a dried purulent exudate. The lips and adjacent buccal membrane were covered with superficial ulcerations with bloody crusts. The heart sounds at the apex were of a poor quality and the pulse was suggestively dicrotic in character. Eight circinate ulcerations covered the glans penis and there was an abundant purulent urethral discharge from an injected meatus. The prostate gland was normal. Both knees were swollen, hot and very tender. There was marked atrophy of both quadriceps femoris muscles.

Laboratory data revealed a urine containing a trace of albumin and loaded with pus cells. There was a moderate normocytic anemia and polymorphonuclear leukocytosis. The Mazzini and gonococcus complement fixation tests were negative. Repeated cultures and smears of the urethral discharge were negative for gonococci.

* From the Medical Service, Veterans Administration Hospital, West Roxbury, Massachusetts. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

April, 1946

March, 1947

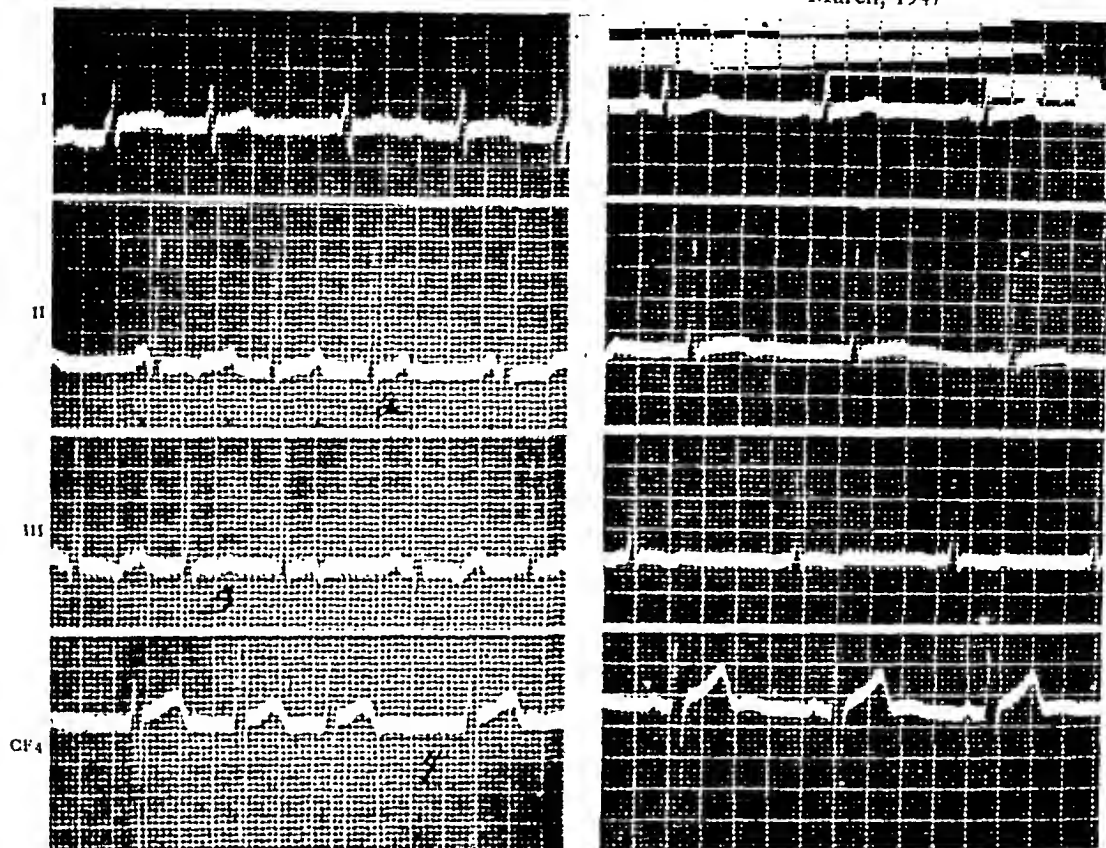


FIG. 1. Case 1. The tracing obtained on admission demonstrates second degree heart block with low or inverted T waves in all leads. The electrocardiogram of March, 1947 is within normal limits.

Numerous blood cultures were sterile. Dark field examinations of the penile ulcers were negative. On April 18th urine cultures were made on ascitic agar media. The same day, under careful aseptic conditions and with the patient fasting, the right knee was tapped and 60 cc. of turbid yellow, cloudy fluid was aspirated and cultures made on the ascitic agar media. Further examination of the fluid revealed a 3 plus clot and 32,500 white blood cells, 87 per cent of which were polymorphonuclears. Sedimentation rates varied from 27 to 29 mm. per hour. Both urine and knee cultures subsequently grew out pleuropneumonia-like organisms, the studies being carried out in the laboratory of Dr. Louis Dienes.²⁷ X-rays of chest and knees were normal. An electrocardiogram (Fig. 1) revealed a P-R interval of .08 to .32 seconds with second degree heart block. The auricular rate per minute was 112 and the ventricular 86, with every third beat dropped. The T waves in leads II and III were inverted. The tracing was interpreted as suggestive of an active myocarditis.

On admission the patient was given penicillin 50,000 units intramuscularly every three hours

for five days without improvement of conjunctivitis, urethritis, arthritis or fever. On April 25th streptomycin 0.5 Gm. intramuscularly every three hours was begun and continued through May 1st. During this period a moderate decrease in temperature to 100°F. and pulse to the 80's occurred together with a disappearance of the urethral discharge. Both knees had been tapped twice previously with removal of 40 to 100 cc. fluid. Further joint effusion did not occur and there was marked symptomatic relief. The conjunctivitis disappeared as did the pyuria and dysuria in the course of the week following cessation of the streptomycin. Repeated urine cultures were negative for pleuropneumonia-like organisms. Subsequently the temperature became normal following treatment of the secondary infection of the penile lesions and an accompanying severe regional lymphadenitis. The patient was most enthusiastic about the progress of his condition in comparison with his previous experience. Objectively it must be emphasized that the most striking improvement occurred during the week after treatment rather than during the week of streptomycin therapy,

and coincidental improvement as part of the natural course of the disease is possible.

He began to be ambulatory on May 20th but the severe atrophy of both quadriceps femoris muscles delayed full activity and required prolonged physiotherapy. Convalescence toward full activity was rapid, with loss of anemia and fall in sedimentation rate to 11 mm. per hour. The patient was discharged well, on July 13, 1946, two and one-half months after treatment with streptomycin.

He returned to his work as a construction laborer in September and remained well until March 10, 1947, when he developed a severe diarrhea. This persisted for five days at which time he returned for examination. Nothing noteworthy was found. An electrocardiogram (Fig. 1) was normal and urinalysis revealed only 1 to 2 white blood cells per high power field in the centrifuged sediment. No stool culture was obtained. On March 18, 1947, pain over the left sacroiliac joint and three days later painful swelling over the right first cuneiform bone were noted. These persisted and he was readmitted to the hospital March 24th. Physical examination revealed nothing beyond these changes, conjunctiva, urethra and prostate being normal. The sedimentation rate was again elevated to 22 mm. per hour but urinalyses, urine and prostatic cultures were all negative. X-rays of the affected joints revealed old mild post-traumatic sclerotic changes. He was given physiotherapy and salicylates for two weeks. During this period he continued to experience pain in back, right foot and, in addition, discomfort and slight swelling in his right knee. His oral temperatures were elevated nightly between 99° and 99.6°F. Although no ocular or urinary signs or symptoms appeared, the joint pains persisted unabated. On April 10, 1947, streptomycin therapy, in dosage of 0.5 Gm. every three hours, was begun and continued until April 20th. All joint pains and fever disappeared during the course of therapy and no side reactions were noted. The sedimentation rate remained elevated. Electrocardiograms taken before and during streptomycin therapy were entirely normal. The sedimentation rate fell to 14 mm. per hour on April 30th and he was discharged from the hospital on May 1, 1947. He was able to return to work the week subsequent to his discharge, and when last seen June 17th was in good health.

CASE II. J. D., a twenty-three year old ex-sailor, was admitted June 14, 1946, complaining

of joint pains, sore eyes and urethral discharge of ten days' duration. The exact date of his last sexual exposure could not be ascertained definitely but was approximately sixteen days prior to onset of symptoms. The triad of complaints appeared simultaneously, the right ankle and hip being the joints involved first, followed in several days by both knees. For four days he had noted chilliness and fever, with severe "canker sores" in his mouth.

There had been a previous attack of balanitis in 1945 and of "rheumatism" at six years of age.

Examination revealed an acutely ill young male in severe distress from joint pain. The temperature was 102°F., pulse 92, respirations 24. Both conjunctivae were injected. There were gray, patchy spots in his mouth covering superficial ulcerations. The foreskin was red, swollen and ulcerated. Partial retraction only could be accomplished but a purulent urethral discharge was evident. Motion was very painful in both knees, right ankle, hip and shoulder. The knee joints contained considerable fluid, more on the left than the right. There was atrophy of the quadriceps femoris muscles.

Laboratory data revealed a urine containing one plus albumin with 10 to 12 white blood cells per high power field in the centrifuged sediment. The leukocyte count was 13,000 with a normal differential count. The Mazzini test was negative. Blood cultures were sterile. Urethral smears and cultures failed to reveal gonococci. The sedimentation rate was 25 mm. per hour on admission and the same rate was noted on July 2nd. Urine culture on ascitic agar on June 20th revealed pleuropneumonia-like organisms, but cultures of straw-colored fluid obtained from both knees were negative. X-rays of the chest and knee were normal.

Penicillin 30,000 units intramuscularly every three hours was started on June 17th and continued until July 1st. Initially there seemed to be some improvement and the temperature fell below 100°F., only to rise again on July 1st. The conjunctivitis cleared during this period and it was not necessary to tap the knee joints again although the patient complained bitterly of joint pain throughout this time. A dorsal slit operation was performed on June 28th to relieve a balanoposthitis. Streptomycin 0.5 Gm. intramuscularly every three hours was begun on July 2nd and continued for seven days. His temperature slowly fell to normal by the end of the week, the urethral discharge ceased and the pyuria cleared. Marked lessening in joint

pain occurred immediately after his treatment had been completed. The patient was allowed up on July 5th and given physiotherapy and special exercises to the atrophied quadriceps femoris muscles. He was walking short distances by July 12th. Recovery was slowed by a *Staphylococcus aureus* furunculosis of the thighs. He was furloughed home on August 3rd, three weeks after completion of the therapy and finally discharged on August 21st. At that time his sedimentation rate was 14 mm. per hour. Follow-up examination on June 7, 1947, revealed that no symptoms had recurred and he had been working steadily. Urinalysis was normal and the sedimentation rate was 5 mm. per hour.

CASE III. L. Z., a twenty-three year old ex-air force lieutenant was admitted May 29, 1946, with a history of urethral discharge and dysuria of three and one-half months' and joint pains of six weeks' duration. On February 14, 1946, nine days after sexual exposure, he had noted purulent urethral discharge. Smears were negative for gonococci and the discharge did not respond to two "courses" of penicillin and sulfonamide tablets. A urologist then treated him with potassium permanganate irrigations and prostatic massage with some diminution in the discharge. However, moderately severe pain on voiding, with urgency, frequency and terminal hematuria developed and persisted. In April both eyes became inflamed and were constantly crusted, this condition lasting about three weeks. For six weeks his hips had been painful and his ankles and right knee had been painful and swollen. For three weeks the left knee had been similarly affected, remaining so until admission. Neoarsphenamine injections at another hospital had not been followed by improvement in joint pain but by lessening in urgency of urination.

Examination revealed a well developed young male who experienced considerable pain in the left knee and both ankles on walking, but otherwise he did not appear ill. The temperature was 99.4°F., pulse 90 and respirations 20. The conjunctivae were normal. Slight urethral discharge was present and the meatus was red. The left lobe of the prostate was irregular but no purulent secretion was expressed on massage. The left knee was swollen and warmer than the right. A small effusion was present in that joint. Both ankles were puffy and painful on weight bearing.

Laboratory data revealed a urine containing a trace of albumin and 70 to 80 white blood cells per high power field. The blood counts were within normal limits. The Mazzini test was negative. Sedimentation rates averaged 21 mm. per hour. A blood culture, urine culture and urine following prostatic massage plated on blood and ascitic agar were all sterile. X-rays of the chest and left knee were normal.

The patient was observed for seven days on symptomatic therapy consisting of salicylates, without improvement in joints or urine. He was started on a week's course of streptomycin 0.5 Gm. intramuscularly every three hours on June 6th. During the week of therapy the urethral discharge disappeared, the urine became negative and the effusion cleared from the left knee. No further elevation in temperature was noted and the patient was completely ambulant with a rare twinge in his ankles. The sedimentation rate was still 19 mm. per hour at the time of discharge from the hospital on June 20th, one week after completion of streptomycin therapy. It was 6 mm. per hour on July 2nd and 7 mm. per hour on August 6th, at the time of follow-up examinations. On those dates the urine was also noted to be free of albumin and white blood cells. The patient then returned to college and when last seen January 3, 1947, had experienced no symptoms suggestive of a recurrence.

CASE IV. D. B., a twenty-three year old college student, was referred to the Veterans Hospital by his college infirmary on May 2, 1947. Approximately two weeks after sexual exposure in 1943 he had noted onset of an urethral discharge. Smears were negative for gonococci and the discharge cleared spontaneously. He was then well until May, 1946, when spontaneous gross hematuria occurred. Investigation failed to reveal any cause for this bleeding. The hematuria recurred on at least three occasions in June and July. In September, after repeated sexual exposures, a purulent urethritis developed; and although smears were again negative for gonococci, the discharge cleared after a week's treatment with penicillin. He was well until the middle of March, 1947, when a purulent discharge with slight dysuria again appeared and persisted in spite of treatment with various urinary antiseptics. Three weeks later marked dysuria, frequency and urgency of urination developed. Coincidentally, there was a painful swelling of the left knee.

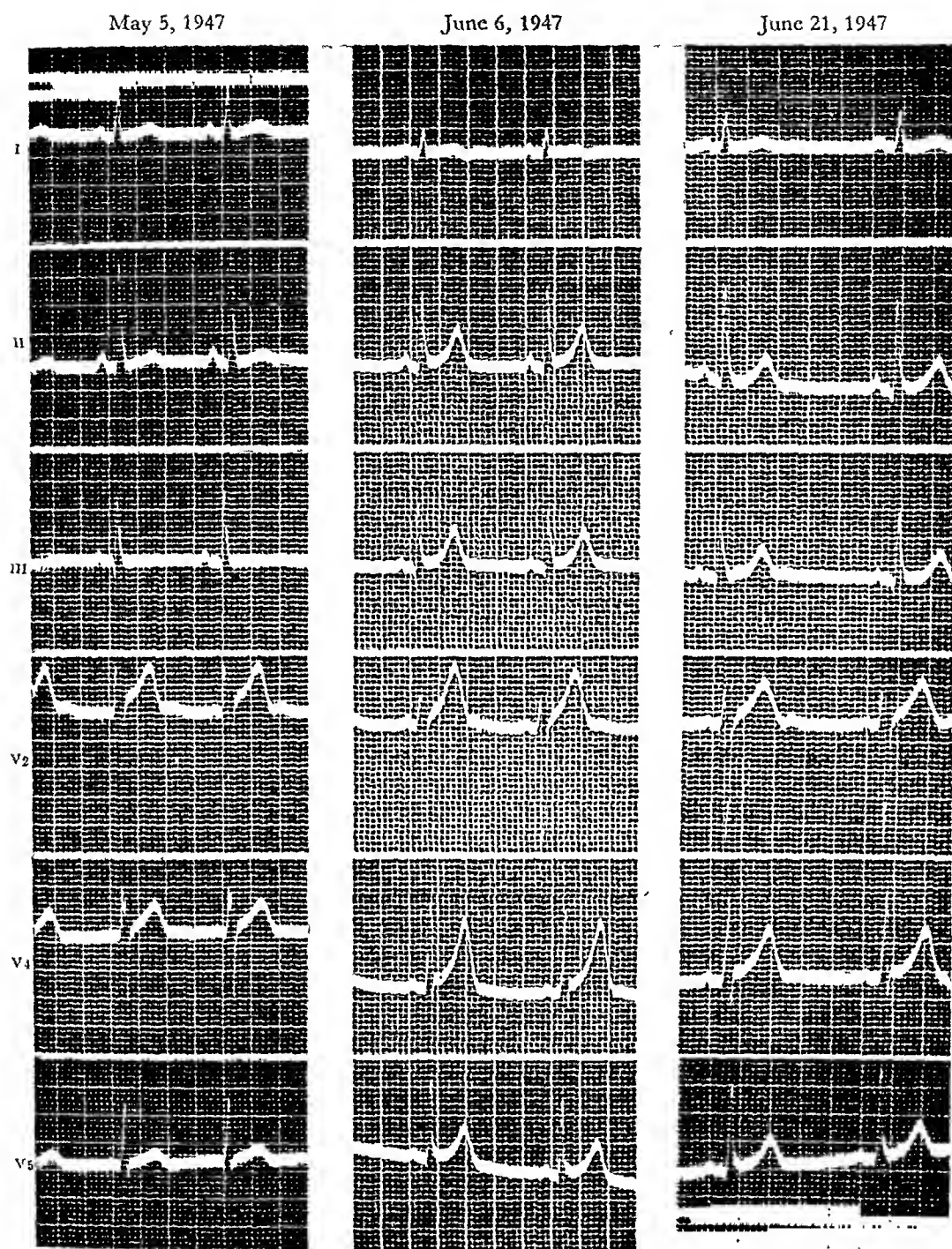


FIG. 2. Case iv. The variations in size of the T waves in all leads, and in the direction of the T waves in lead I are shown during the periods of acute illness, convalescence and clinical recovery.

Later the right knee became involved and he was hospitalized at his college infirmary with a high fever. No cultures for *L* organisms were carried out either on the urine or synovial fluids. On April 20th he was started on a course of penicillin, 50,000 units every three hours. Three days later it was noted that he had developed a moderate bilateral conjunctivitis

which persisted. The dysuria cleared rapidly but the knees continued to be painfully swollen, and the pyrexia of 101° to 102°F. was unaffected up to his admission.

Examination revealed an acutely ill, pale young male, obviously experiencing pain on motion of his knees. The oral temperature was 100.6°F. , pulse 90, respirations 20. A moderate

injection of the conjunctivae with a dry exudate was present. No urethral discharge was detectable. The prostate gland was not abnormal. Both knee joints were swollen, of normal temperature and very painful on motion.

Laboratory examinations disclosed a normal urinalysis. The hemoglobin was 77 per cent, the red blood cell count was 3,560,000 and the white blood cell count was 8000. A sedimentation rate was 33 mm. per hour. X-rays of the knees and chest were not illuminating. Cultures of urine and synovial fluid obtained from the right knee joint failed to grow any bacterial organisms. Repeated electrocardiograms revealed variations in the size and direction of the T waves in leads I, III and V_6 , suggestive of an active myocarditis. (Fig. 2.)

On May 3rd treatment with streptomycin 0.3 Gm. every three hours was instituted and continued for ten days. The conjunctivitis cleared promptly but he remained febrile for seven days. During the last three days of therapy a dramatic improvement in his joint swelling and pain occurred, with complete disappearance of the synovial fluid and he was granted a leave of absence to complete his collegiate examinations on May 14th.

Re-examination on June 4, 1947, demonstrated only minimal residual swelling in the left knee although he had been much more active than he had been instructed to be. The electrocardiogram revealed further increase in the deviations of the T waves from normal. The sedimentation rate was 23 mm. per hour. He was placed on a regimen of restricted activity and by June 21st the left knee appeared normal. The electrocardiogram had returned to normal. His anemia disappeared and the sedimentation rate had fallen to 8 mm. per hour. He was discharged from the hospital on June 22, 1947 and was well when last seen on February 18, 1948.

COMMENT

Etiology. Reiter¹ associated the disease with a spirochetosis but recent reports have failed to substantiate this concept. Later continental descriptions commented on the association of the syndrome with attacks of bacillary dysentery. Manson-Bahr¹⁴ believes that the disease is the "familiar dysenteric polyarthritis." Recent letters and comments^{17,18,20,21} from a series of physicians who had served in the Middle East during

the war indicate that a similar syndrome was not uncommon as a late sequella of Shiga or Flexner dysentery. Short,²² in an excellent discussion of arthritis occurring in the American Forces in the Mediterranean Theater, concluded that the syndrome triad occurring after bacillary dysentery and Reiter's syndrome were probably the same infection. Short further believed that the dysentery merely activated or provided a portal of entry for the etiologic agent, and that post-dysenteric arthritis was due to a secondary invader, not to the dysentery bacillus. In support of this hypothesis he advanced the facts that certain chemotherapies, while most effective in treatment of the dysentery, were ineffective in arthritis, that no *Shigella* group organisms had ever been recovered from joint fluids and that the pathologic findings of the synovia were consistent with those found in cases of non-dysenteric Reiter's syndrome. Others¹⁹ believe that several types of the syndrome exist, one of which has a viral etiologic agent.

Dienes and Smith^{23,20} were the first to suggest that a relationship might exist between certain types of arthritis, Reiter's syndrome and the pleuropneumonia-like organisms (L organisms). This group of organisms was first isolated from cattle by Nocard and Roux in 1898. Klieneberger renewed interest in them in 1935 by isolating numerous strains from rats infected with *Streptobacillus moniliformis*. Since that date Sabin²⁴ and many others have studied the various strains and the possible similarities between the polyarthritis produced by them in mice and human rheumatoid arthritis. Dienes^{26,27} has described these organisms extensively and believes that they should be classified as bacteria in a separate group close to *Hemophilus*. They are not found commonly in the respiratory or gastrointestinal tract. Vallee¹¹ has discussed the above findings and others at length. Wallerstein, Vallee and Turner²⁵ have reviewed the possible relationship of the pleuropneumonia-like organisms to various types of arthritis and ulcerative colitis by

means of agglutinations of various serums against one strain of such organisms. Significant titers were found only in cases which had as presenting symptoms two of the three findings in the Reiter's triad. Lever and Crawford³ attempted unsuccessfully to culture pleuropneumonia-like organisms from the secretions in one case. Dienes and Smith³⁰ reported four cases of Reiter's disease from whom positive cultures for L organisms were obtained from the prostatic fluids and two from synovial fluids.

The isolation of pleuropneumonia-like organisms from the urine and joint fluid of Case I when he was at the height of his first recurrence, and from the urine of Case II during the most severe period of his disease, strongly supports the suggestion of an etiologic relationship made by Dienes and Smith. The failure to repeat these findings after streptomycin treatment, or in a late, subsiding case, such as Case III, is not greatly disturbing. The inability to isolate the L organisms in Case IV, on the other hand, is unfortunate although signs of urinary tract infection were never present during our observation. Many investigators have noted that numerous strains of L organisms exist. This fact might help explain the variations in the severity and course of the syndrome and the variable ease of cultivation of them.

Our histories indicate that the channel of invasion was through the urogenital tract, contact having occurred by sexual intercourse. Symptoms appeared nine to sixteen days after exposure. Pyuria was a prominent finding. While Reiter's syndrome has not definitely been reported as occurring in females, the presence of pleuropneumonia-like organisms in the female genital tract has been frequently shown to occur in women with only mild or moderate gynecologic complaints.^{23,28,29} The finding of an organism that apparently produces a severe systemic disease in males but only a local genitourinary infection in females is a most interesting one. Further studies on this observation might prove of value.

Cardiac Complications. Lever and Craw-

ford's³ first patient apparently died from some cardiac disorder but no autopsy was performed. Feiring¹³ reported prolongation of the auricular-ventricular conduction in two cases. Our Case I presented a markedly prolonged P-R interval, with second degree heart block and inverted T waves in lead II, accompanied clinically by poor heart sounds. These findings suggested the presence of an acute myocarditis. Following treatment the electrocardiogram, heart rhythm and sounds became normal. Case IV presented no clinical cardiac abnormalities other than electrocardiographic T wave deviations in leads I, III and V₅. These became manifest only after treatment when the remainder of his clinical course had demonstrated vast improvement. Unfortunately, cardiac studies were not made in Cases II or III. These should be carried out on future patients as the present evidence is inadequate to determine the nature or extent of the myocardial damage.

Treatment. In the treatment of this syndrome nearly all available types of medication have been tried. Of these, fever therapy has been reported as successful by Strachstein⁸ and Beiglbock.¹⁴ Sargent¹⁰ believed that typhoid vaccine was of benefit in the cases with eye complications. Neoarsphenamine, iodides, salicylates, sulfonamides and penicillin in turn have been used without striking effect. Gold salts have been used unsuccessfully by Baxter²⁰ and others. An analysis of forty-four cases recently reported in the American and British literature indicates that Reiter's syndrome is an infection presenting a variable course which may be short, long-standing or relapsing. Therefore, the effect of a given therapy, unless it is dramatic, is difficult to interpret. The analysis also indicates the average duration of a single attack of the syndrome to be four months. The minimum duration was twelve days and the maximum nine months. Recurrences were found in approximately 30 per cent of the cases, occurring from one to thirty months after the initial apparent recovery. Cases recurring

intermittently over eleven and fifteen years have been recorded.

We were led to try streptomycin* because of the earlier reports suggesting a relationship of the disease to organisms of the gram-negative bacillus variety. In addition, Dienes^{26,27} and others had noted that certain variant forms of gram-negative organisms such as *Streptobacillus moniliformis*, conceivably susceptible to the antibiotic, were morphologically similar to the pleuropneumonia-like organisms. The organisms' classification near the susceptible group *Hemophilus* has been noted. No *in vitro* studies were made by us in respect to the effect of streptomycin on subcultures of the organisms obtained from the urine or synovial fluids. Our clinical experience, however, in the streptomycin treatment of chronic prostatitis due to infection with the L organisms had been so striking that we were anxious to try it in a possible systemic infection with the same organisms.

The daily dose of 4 Gm. of streptomycin for seven days was believed to give adequate concentration of the drug for a significant period of time. One patient treated with 2.5 Gm. per day for ten days did equally well. Longer treatment periods were not feasible because of the limited supply of the antibiotic. No reactions attributable to the drug were noted.

Our Case I had originally relapsed four months after apparent recovery from the initial attack which had been of eight months' duration. Following a week's therapy with streptomycin two and a half months of hospitalization were necessary for complete recovery, although fully half of this was required for the application of physiotherapy to the atrophied quadriceps femoris muscles. Eleven months after this he experienced what was probably a relapse. Re-treatment with streptomycin at that time effected a prompt recovery. No definite conclusions can be drawn from

this. Case II was given a trial of other medication before instituting streptomycin. During this period some improvement had occurred, but a relapse with increase in severity of symptoms associated with the recovery of pleuropneumonia-like organisms in the urine culture suggested a trial of streptomycin. Within two weeks of the institution of this therapy, marked amelioration in fever, urinary and joint symptoms had occurred. This again may have been the natural course of what was a milder disease than was apparent clinically. He has remained well for a year since treatment. Case III experienced a dramatic improvement while on streptomycin, but unfortunately a positive L-organism culture had not been obtained and the case was already of three and one-half months' duration. The possibility that the infection was waning and that mere hospitalization alone might have been sufficient to produce the striking improvement must be considered. Case IV responded strikingly in regard to fever and joint swelling, but the electrocardiographic changes appeared during and were most marked after treatment.

In conclusion it must be recognized that the disease may run a prolonged and disabling course. Our patients treated with streptomycin were returned to full activity considerably sooner than the average of the recently reported cases. It cannot be denied that this may have been coincidental, nor is it certain that sufficient time has elapsed to be sure that other recurrences will not appear. There was, however, a consistent prompt improvement in the genitourinary symptoms and signs during or immediately after treatment. The lack of serious joint or eye complications in our four cases also seems more than fortuitous. The results are sufficiently promising to warrant the further use of this antibiotic in other cases of this syndrome.

SUMMARY

1. Four additional cases of Reiter's syndrome are presented. In two of these pleuropneumonia-like organisms were ob-

* The author wishes to acknowledge the interest and cooperation of the Streptomycin Committee, Veterans Administration, Washington, D.C., which supplied the streptomycin.

tained from the urine and in one from the knee effusion fluid. This is in accord with the previous findings of Dienes and Smith who have suggested that an etiologic relationship may exist between this group of organisms and the syndrome.

2. The electrocardiographic and cardiac abnormalities in two cases are noted, and previous observations regarding cardiac complications are briefly discussed.

3. Three patients were treated for seven days with a total daily dose of 4 Gm. of streptomycin; the fourth patient received 2.5 Gm. a day for ten days. The results were not conclusive but sufficiently encouraging to warrant further use of this therapy. No untoward effects of treatment appeared.

The author wishes to express his gratitude to Dr. Louis Dienes of the Massachusetts General Hospital for performing the cultures in Case 1 and for his generosity in instructing us in the technique of such cultures. The helpful suggestions of Drs. Marian Ropes and Walter Bauer of the same hospital are also gratefully acknowledged.

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Clinical Value of Examination of the Gastric Contents for Tubercle Bacilli*

ANDREW L. BANYAI, M.D.

Milwaukee, Wisconsin

TO Mcunier¹ belongs the credit for being the first to advocate and practice examination of the gastric contents for tubercle bacilli. This method, however, was not accepted for general diagnostic use until the publication of the studies of Armand-Delille and Vibert² in 1927. Since then a great deal of thought has been given to evaluation of this procedure. In patients with parenchymal pulmonary tuberculosis who do not expectorate or who have negative sputum, tubercle bacilli were found in the gastric contents in 60 per cent of the cases studied by Gad,³ in 55 per cent of Gullbring and Levin's cases⁴ and in about 20 per cent of the cases of Ulmar and Ornstein.⁵ In children with pulmonary tuberculosis (parenchymal or hilar), Opitz⁶ found tubercle bacilli in the gastric contents in 93 per cent, Bocr⁷ in 73 per cent and Langer⁸ in 40 per cent. Gourley⁹ examined 210 tuberculous children and found that the gastric contents were positive for tubercle bacilli by guinea pig inoculation in 40 per cent. An excellent review of the pertinent literature up to 1937 is available in her communication. The investigations of Stiehm¹⁰ revealed the significant fact that 71.4 per cent of his patients with minimal pulmonary tuberculosis and negative sputum had gastric aspirations positive for tubercle bacilli. Roper and Ordway¹¹ reported that by the addition of gastric lavage to examinations of sputum, positive recovery of tubercle bacilli was doubled in newly admitted tuberculous patients. In a

similar group of patients, Robinson and Dunn¹² found that 29 per cent of the individuals examined gave positive results by gastric lavage. The positive bacteriological findings varied according to the stage of the disease in their cases; 23 per cent positive in patients with minimal tuberculosis, 27.5 per cent in the moderately advanced and in 36 per cent in the far advanced groups. They recorded 32 per cent positive findings in the gastric contents of patients who had no expectoration.

I have been using gastric aspirations in my practice since 1933. During this period, the value of this procedure has become more and more evident. On the basis of my own experience as well as of others, I am convinced that bacteriological examination of the fasting gastric contents can be used to advantage in tuberculosis work for the following purposes: (1) In clinical diagnosis in institutional as well as in private practice; (2) for the management of tuberculous patients who are treated by bed rest or by some form of pulmonary relaxation therapy; (3) in follow-up examinations of patients who presumably recovered from tuberculosis; (4) for bacteriological screening of individuals who had close contact with persons suffering from tuberculosis, and (5) for the study of individuals who are found to have abnormal findings in their chest roentgenograms taken during mass surveys, whenever such lesions suggest the possibility of active tuberculosis.

Securing gastric specimens for bacterio-

* From the Department of Medicine, Marquette University Medical School, Milwaukee, Wisconsin.

logical examination is a simple procedure that can be performed by the physician, by a trained attendant or by a laboratory technician. It is preferable to aspirate the gastric contents rather than to wash out the stomach. Aspirations are done on five successive mornings as soon after rising as feasible. In Poulsen and Andersen's¹³ investigation of 199 tuberculous children, tubercle bacilli were recovered from the gastric contents in 77 per cent on the first examination, in 96 per cent after the second examination, and in 100 per cent when five gastric specimens were examined. My findings are in harmony with these observations.

The fasting gastric contents are aspirated by means of a sterilized No. 16 French nasal catheter. Smaller tubes are used in children and in infants. The tube is passed through the nose readily if its tip is moistened with sterile glycerine. It can easily be maneuvered through the nasal cavity, even in the presence of minor submucous bony deformities or of septal deviations. As soon as the tip reaches the pharynx, the patient is instructed to swallow repeatedly while the tube is passed down the esophagus. There is very little discomfort from this procedure and the patients readily accept repeated gastric aspirations. By means of a 10-cc. or 20-cc. glass syringe, the gastric contents are removed and are collected in a sterile container.

For some years, it has been the routine in my practice to pool individual gastric specimens obtained on successive days. The pooled specimens were prepared for culture or animal inoculation as a single specimen. This was done with the assumption (1) that the end results are better than when examining individual samples separately, and (2) that keeping the gastric contents in the refrigerator until all specimens of the series are collected does not influence the outcome of the examination unfavorably.

Recently, however, considerable doubt

has arisen concerning the soundness of this practice in view of the possible harmful effect of the human gastric juice upon the tubercle bacilli. The first report dealing with the latter subject was published by Falk.¹⁴ He observed that tubercle bacilli remained viable and virulent in spite of their exposure to gastric juice. Similar observations were made by Cadeac and Bourney¹⁵ in their feeding experiments on dogs. They noted the survival of virulent tubercle bacilli twelve hours after feeding to animals in food mixtures. More recent and more accurate research studies relative to this question, however, brought out contrary results. The work of Floyd and Page¹⁶ is of particular interest in this respect. They added a suspension of virulent tubercle bacilli to 15 cc. of artificial gastric juice and incubated it at body temperature for three-, six- and twelve-hour periods. Following incubation, the mixture was neutralized and inoculated into guinea pigs. The experimental animals developed tuberculosis the extent and severity of which was more or less proportionate to the length of exposure of the tubercle bacilli to the gastric juice. The tuberculous lesions in the six-hour group were about one-half of those found in the group inoculated with tubercle bacilli after three-hour digestion with gastric juice. The lesions were nearly 80 per cent less in the twelve-hour group than in animals inoculated with the three-hour specimen. Corroborative pertinent findings were noted by Kramer¹⁷ in his investigations. He mixed 40 cc. of normal human gastric juice with 5 cc. of sputum of tuberculous patients and kept the mixture incubated at body temperature. The mixture was shaken from time to time so as to simulate the motion of the stomach. Guinea pigs were inoculated with 2 cc. of this mixture after incubating for one, four, ten, twenty-one, forty-five and sixty-eight hours. Two and a half months after inoculation, the animals

were sacrificed and anatomical, histological and bacteriological examinations were carried out. It was observed that tubercle bacilli present in the sputum began to lose their pathogenicity in ten hours. After twenty-one hours, their capacity to induce tuberculosis in guinea pigs was entirely lost. The loss of virulence of the tubercle bacillus is not due to hydrochloric acid. Inkster and Gloyne¹⁸ observed that mixing sputum positive for tubercle bacilli with gastric juice of high acidity (62 degrees) did not destroy the virulence of these micro-organisms. Roper and Ordway¹¹ demonstrated that the viability of human tubercle bacilli was not affected by free hydrochloric acid up to tenth-normal strength even after forty hours of exposure (the normal fasting stomach usually contains free hydrochloric acid in concentrations less than twentieth-normal). In view of these findings, it is advisable not to pool specimens suspected of containing tubercle bacilli. Instead, the aspirated gastric contents should be examined individually as soon as possible after removal from the stomach.

The technic of preparing gastric specimens for culture has been used in the overwhelming majority of my cases. Experience has shown that tubercle bacilli are detectable by this method as reliably as by animal inoculation. This observation is in harmony with the experimental studies of Corper.¹⁹ He proved nearly twenty years ago that the culture method was as efficient as guinea pig inoculation for the detection of tubercle bacilli. Corper pointed out the added advantage of the culture method in that the growth of tubercle bacilli on culture medium is not affected by the virulence of the micro-organism. At the same time, in contrast to animal inoculation, one does not have to reckon with the possible natural resistance of the animal body. It is a well known fact that tubercle bacilli of lowered virulence may not produce tuberculosis in the guinea

pig. The culture method is, of course, simpler and less expensive. On very rare occasions, one may find non-pathogenic acid-fast bacilli in the gastric contents. These can be identified readily by their morphological, tinctorial and colonial characteristics, and, in case of doubt, by guinea pig inoculation. Claims for the usefulness of cultures are put forward with the full realization that in some instances it is extremely difficult or impossible to grow tubercle bacilli from the aspirated gastric contents. Occasional failure of this procedure is not to be attributed to anything but to unavoidable technical limitations or perhaps, to the lowered viability of the micro-organisms.

Since the time I began to resort to bacteriological examination of the gastric contents, it became obvious that the concentration method is unreliable. Even more unreliable is examination of a simple smear. To illustrate this point, it may be mentioned that of 783 gastric specimens positive for tubercle bacilli by culture there were only 147 positive by the concentration method (18.7 per cent) and only sixty-eight were positive on simple smear (8.6 per cent). Simultaneous examination of a gastric specimen by culture and guinea pig inoculation does not always give identical results. Discrepancies between these two methods have been noted on repeated occasions. From the same material, culture may give positive results while guinea pig inoculation reveals no evidence of tuberculosis, and vice versa. The explanation of such differences should be sought in the following possible factors: (1) The tubercle bacilli in the specimen are so attenuated that they are incapable of infecting a guinea pig, or they lose their viability during the process of preparation for the culture. (2) There may be so few tubercle bacilli present in the gastric specimen that the portion of the gastric sample used for culture or animal inoculation does not contain micro-organisms. As

is well known, a similar situation often arises when two guinea pigs are inoculated with the same material at the same time. (3) Using more centrifuged sediment for one test than for the other may lead to contradictory results.

The technic of preparing cultures from gastric specimens, as previously reported by Anderson,²⁰ is as follows: Enough potassium hydroxide solution is mixed with the material to make a concentration of 1.5 per cent hydroxide, and the mixture is kept at 40°C. for thirty minutes or long enough to become warm. The liquefied specimen is centrifuged at high speed for twenty minutes, decanted and resuspended in a few cc. of physiological saline solution. A drop of brom-cresol-purple solution is added before neutralizing with 5 per cent hydrochloric acid. By pouring off the fluid before the addition of acid, one avoids reprecipitation of the protein. Keeping the solids finely divided results in a more evenly distributed culture. The neutral residue is washed and centrifuged in about 40 cc. of physiological saline solution; after this, it is ready for culture. As a rule, the entire sediment is used for this purpose, dividing it among three slants of a modified Petragani's medium in oval test tubes measuring 155 by 27 by 17 mm. The tubes are incubated in a nearly horizontal position until no moisture is visible on the surface of the medium (usually forty-eight hours). The tubes are then sealed with a mixture of two parts of paraffin to one part of vaseline, and incubated in the upright position until evidence of bacterial growth is noted, or for a maximum period of eight weeks. The cultures are examined grossly every week. When macroscopic growth appears, smears are prepared for examination on any first growth and as often thereafter as necessary for establishing accurate identification of the micro-organism. Preparations from cultures are best stained individually so as to

avoid possible contamination of negative slides in the same batch. Alcoholic solution of carbol fuchsin, with a few crystals of pure sodium chloride sprinkled over the dye, is preferable to steaming over flame. It is common to find only one culture medium out of three with bacterial growth. Usually, fewer than five colonies are seen, although colonies numbering between five and ten, or even more, may occur. Whenever the cultural growth, as observed grossly or microscopically, appears to vary from usual, it is tested by subculturing to ascertain whether or not the micro-organisms grow at room temperature or have the ability to grow in the incubator in a shorter period of time than that required by the tubercle bacillus. The earliest positive colonies appear in about sixteen days. The largest number are noticeable between the twentieth and twenty-third day. Approximately 90 per cent of the positive cultures are reportable by the end of the fifth week. The average length of time required for positive culture is twenty-five days.

Concerning the origin of tubercle bacilli found in the fasting gastric contents, the following points deserve consideration:

1. The ingestion of tubercle bacilli can be excluded with reasonable certainty because the patient is not permitted to take nourishment during the night and morning preceding the gastric aspiration. Furthermore, it is unlikely that viable bacilli will be found in milk from tuberculin-negative herds (tuberculosis in cattle has been virtually eradicated throughout the United States) or in milk which has been pasteurized.

2. The question might arise as to the likelihood of finding tubercle bacilli in healthy individuals who have been exposed to tuberculosis incidentally or professionally (physicians, nurses and hospital and sanatorium attendants). It has been my experience, and this coincides with the observations of others, that tubercle bacilli are never

found in the fasting gastric juice of healthy persons or of those with non-tuberculous pulmonary diseases.

3. Clinically manifest tuberculosis of the tonsils as a source of tubercle bacilli in the aspirated stomach contents is extremely rare, even in patients with long-standing, far advanced pulmonary tuberculosis. According to Rather,²¹ microscopic examination revealed active tonsillar tuberculosis only thirty-five times in 19,000 tonsillectomies. This is equivalent to 0.18 per cent, a percentage which is much lower than the incidence of significant reinfection tuberculosis of the lung currently found in mass roentgenological surveys in this country.

4. The rôle of tuberculosis of the stomach as a source of tubercle bacilli is insignificant. In a series of 1,043 necropsies of tuberculous patients, Cullen²² noted tuberculosis of the stomach in four cases (0.38 per cent). A similar study by Kabuki²³ revealed only a 0.11 per cent incidence of gastric tuberculosis, while Browne and his associates²⁴ reported thirty cases out of a group of 1,321 necropsies in patients who died of tuberculosis (0.22 per cent). In a series of 10,000 postmortem examinations, Collinson and Stewart²⁵ found only three cases of gastric tuberculosis (0.03 per cent). Gentile²⁶ reports a collective review of Mirolli,²⁷ covering postmortem findings in 71,871 cases, which showed an incidence of 0.21 per cent. Sullivan, Francona and Kirshbaum²⁸ recorded only two cases of tuberculosis of the stomach in 11,480 postmortem examinations (0.01 per cent). In both of these cases, evidence of active tuberculosis was found in the lungs. They found no gastric tuberculosis in necropsies of more than 10,000 non-tuberculous individuals. Also, they report that during the period from 1929 to 1938 only one case of tuberculosis of the stomach was encountered in 75,000 surgical specimens.

5. Regurgitation of tubercle bacilli-bearing

intestinal juices into the stomach in case of intestinal tuberculosis is unlikely. Duodenal tuberculosis is exceptionally rare. Moreover, tubercle bacilli are easily demonstrable in the sputum of patients whose pulmonary tuberculosis is complicated by intestinal tuberculosis.

6. There is a very rare possibility of finding tubercle bacilli in the stomach as the result of perforation of a tuberculous mediastinal lymph node into the esophagus.

7. Tuberculosis of the nasopharynx in persons who have no demonstrable pulmonary tuberculosis is extremely rare and therefore has no clinical significance in this respect.

Possible sources of tubercle bacilli in the fasting gastric contents are as follows:

1. Frank tuberculous infiltration of the lung parenchyma, of the reinfection type or primary type, readily demonstrable on physical examination or roentgenogram.

2. Tuberculous hilar lymph nodes, which always signify a previous coexistent primary or reinfection-type lesion in the lung parenchyma, may discharge tubercle bacilli into the adjacent bronchi.

3. Active tuberculous lesions of the lung parenchyma, or tuberculous lymph nodes which may appear well fibrosed or calcified in the roentgenogram.

4. Active tuberculous foci in the lung or lymph nodes, which are not visualized on a standard postero-anterior roentgenogram of the chest, may be sources of tubercle bacilli found in the stomach. The difficulty in visualizing these lesions is due to the fact that they are localized in areas obscured by the heart shadow, the mediastinal structures, the dome of the diaphragm or by the bone structures of the thoracic cage.

5. Tubercle bacilli may originate from hidden or manifest tuberculous involvement of the bronchi and bronchioles, with or without secondary bronchiectasis.

6. Tubercle bacilli may originate from

lesions in the lung which cannot be visualized roentgenologically because their consistency is such that they do not cast a shadow when exposed to roentgen rays.

7. Minute lesions may be sources of tubercle bacilli. These lesions may not be observed roentgenologically either because of their small size or because of the absence of perifocal inflammation and edema.

With these considerations in mind, the following pointers are offered as possibly serviceable guides in every-day practice:

1. Assaying a pulmonary lesion from the diagnostic standpoint is a composite task and proper evaluation of the relevant components is of utmost importance. The diagnostic value of roentgenological findings should not be overestimated. The well known roentgenological similarity of various etiologically unrelated diseases supports this attitude. Grave errors may be committed when the diagnosis is based on the roentgenological appearance alone without due regard to other clinical and laboratory data. Although interpretation of the x-ray shadows is an important adjunct in this work, it is not nearly as essential as the bacteriological identification of the disease.

2. Examination of the fasting gastric contents for tubercle bacilli is indispensable, regardless of the apparent stage and extent of the disease, if the tuberculous patient does not expectorate or if the sputum is not acceptable for competent examination. Of course, there is more frequent need for gastric aspirations in minimal cases than in patients with far advanced pulmonary tuberculosis. But I have recorded the absence of cough and expectoration many times in patients in whom the diagnosis of far advanced tuberculosis was established beyond the shadow of a doubt. Unquestionably, similar observations have been made by others who have the opportunity to scrutinize the pulmonary status of a large number of individuals. As an example, I may refer

to one of my patients seen recently. He was a white man, aged forty-nine years, who was ailing for several months with fever, night sweats, malaise and loss of weight. The family history was non-contributory and the past history was irrelevant. His temperature was 101.8°F. The physical findings were of no significance except with respect to the chest. Here there were signs of pulmonary infiltration over the upper two-thirds of the right lung and over the lower one-half of the left lung. The roentgenogram of the chest revealed the following findings: Right side: uniform pleural thickening with an underlying exudative process throughout, with a large cavity in the middle one-third. Left side: exudative lesion limited to the lower two-thirds. The patient had no expectoration. The diagnosis was established on the basis of gastric aspirations which revealed the presence of tubercle bacilli.

3. The number of gastric aspirations indicated is determined by the reasonableness of the suspicion of tuberculosis and varies from five to as high as fifteen. The greater the weight of circumstantial evidence, the greater should be the number of gastric aspirations. Points which should prompt a thorough bacteriological survey include: (1) History of exposure to a known case of tuberculosis; (2) previous pleurisy with effusion. It is estimated that 75 per cent of so-called idiopathic pleural effusions are tuberculous in origin and that approximately 50 per cent of the patients with this condition develop manifest pulmonary tuberculosis subsequently. (3) Pulmonary hemorrhage some time prior to the presenting illness; (4) extrapulmonary forms of tuberculosis in the past; (5) history of ischio-rectal fistula; (6) chronic malnutrition; (7) silicosis; (8) asbestosis; etc.

4. Roentgenological findings do not always serve as reliable guides to the course of the tuberculous process. Often the lesion

may appear fibrosed or apparently calcified, remain stationary and suggest complete healing. Bacteriological examination of the fasting gastric contents, however, may reveal tubercle bacilli in some of these cases. This brings to mind the saying so often appropriate in the management of pulmonary tuberculosis, namely, "treat the patient and not the x-ray shadow." In such instances one should insist on periodically repeated examinations of the fasting gastric contents until it is found that they are consistently negative for tubercle bacilli. This is mandatory for the sake of the patient as well as for the sake of his environment. If this principle is disregarded, the patient may be released as cured when actually he is still suffering from active tuberculosis. Individuals who subsequently come in close contact with him will be exposed to the danger of infection with tubercle bacilli. In other words, a patient of this type becomes an unrecognized or unadmitted tuberculosis carrier.

5. During the course of certain artificial relaxation therapy measures, the interpretative inspection of the diseased lung, with the aid x-ray is virtually without value or it is a technical impossibility. Measures such as artificial pneumothorax, thoracoplasty, extrapleural pneumothorax, paraffin plumbage and oleothorax induce a degree of pulmonary relaxation which *a priori* obscures the lung field where the lesion is localized. It may either be impossible or impracticable to attempt to re-expand the relaxed lung. A competent assessment of pathological changes, of their progression or retrogression cannot be made by visual means. At the same time, in consequence of the relaxation therapy, the patient ceases to cough or is not raising sputum satisfactory for bacteriological examination. The search for tubercle bacilli in the gastric contents is the only means at our disposal in such instances with which to gauge the recovery of the

patient. When dealing with this problem, due consideration must be given to the rate of healing of the tuberculous process. It may take a period of one to two years before a patient with previously positive gastric specimens becomes negative for tubercle bacilli by this method. As an example, I may mention a patient of mine, a young woman with far advanced pulmonary tuberculosis who was treated by thoracoplasty. At completion of the procedure her sputum was positive for tubercle bacilli. Three months later, the sputum was negative but the subsequently examined gastric contents revealed the presence of tubercle bacilli. The patient became consistently negative when examined by gastric culture after the eighth month postoperatively. Altogether, this patient had fifteen examinations of gastric aspirations for tubercle bacilli, two months apart, following thoracoplasty and before she was classified as an apparently arrested case of tuberculosis.

6. The interval between gastric aspirations depends upon the character of the disease, the type of treatment applied, symptomatic and semeiological responses to treatment, and on objective findings noted on periodic examinations. It is well to bear in mind the limitations of small numbers of examinations. A pertinent case is that of a twenty-two year old patient of mine with minimal pulmonary tuberculosis and positive sputum. On strict bed rest, the sputum was converted to negative in four months. At this time, the gastric contents were also negative for tubercle bacilli. In spite of this, on the basis of an individual evaluation of this case, the patient was considered still to have active tuberculosis. For this reason, his rest regimen was continued. Our clinical judgment was vindicated subsequently when examination of the stomach contents three months later showed the presence of tubercle bacilli. Only when two additional sets of five gastric specimens were

found negative, two months and four months later, respectively, was the patient considered an apparently arrested case of pulmonary tuberculosis.

7. During the course of treatment of a tuberculous patient, the significance of the result of a single examination of the gastric contents must be interpreted with a great deal of caution and circumspection. This warning is offered on the basis of the experience that, not infrequently, a sample aspirated from the stomach may prove negative for tubercle bacilli while one taken the next day is positive. The acceptance of a single negative report as conclusive is bound to invite regrettable consequences. As an illustration, I wish to give the salient data from the record of one of my patients. She had moderately advanced pulmonary tuberculosis, with limited disease in each lung. At the time of her admission, the first gastric specimen was positive but the gastric contents obtained the next day were negative. Following three months of strict bed rest, converse findings were recorded on two successive days. Two and a half months later, a similar notation was recorded. At this time artificial pneumothorax was instituted on the more involved side. After six months' pneumothorax treatment, examination of the gastric contents was negative. However, tubercle bacilli were recovered from the aspirated material obtained on the following day. In view of past experiences, it was deemed advisable to carry on with pneumothorax treatment. This decision was followed by finding two negative gastric specimens three months later and a positive specimen two months thereafter. At this time, in view of roentgenologically demonstrable honeycomb cavitation in the lung opposite to the pneumothorax side, an extrapleural paraffin pneumonolysis was done to obliterate these cavities. The patient was kept on a rest regimen and on graded exercise for an additional twelve

months. During this period, she had fifteen gastric aspirations (three series of five each). All these having been negative, the patient was classified as an apparently arrested case of pulmonary tuberculosis.

8. Examination of the gastric contents may serve as a useful index in determining the patient's exercise tolerance following prolonged bed rest or major thoracic surgery. It is a matter of common knowledge that minute changes resulting from a flare-up of a tuberculous process may not be visualized on the roentgenogram and may easily escape detection on physical examination. Also, it is known that certain forms of reactivation or progression of the disease may cause no symptoms whatever. In the past, because of these limitations in our ability to assay the patient's condition, many disastrous errors in judgment were committed by permitting too early or too much exercise. In gastric aspirations we have a reliable and sensitive means at our disposal for regulating the patient's activities and for ascertaining reactivation of the disease long before it becomes visible on the x-ray film.

9. The bacteriological examination of the fasting gastric contents is far superior to the erythrocyte sedimentation test in ascertaining whether a tuberculous process in the lung is active or healed. All in all, it is my impression that the clinical value of the erythrocyte sedimentation test in tuberculosis is greatly overestimated. A study of the sedimentation rate of the red blood cells in approximately 10,000 tuberculous patients seen in my practice revealed that 8 per cent of them had normal values. Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in those with a reinfection type of the disease. The erythrocyte sedimentation rate does not parallel the type and extent of tuberculosis.

Normal rates were encountered in association with minimal, moderately advanced and far advanced infection, with productive and with exudative pulmonary tuberculosis and with solitary and multiple cavities. The size of the pulmonary cavities varied from honeycombing to cavities 45 mm. by 70 mm. in diameter. Aspirated gastric contents positive for tubercle bacilli were encountered in association with normal sedimentation rates on frequent occasions.

10. I have called attention, in previous communications,²⁹ to the importance of bacteriological examination of the fasting gastric contents in extrapulmonary forms of tuberculosis. In a group of twenty-two patients with bone and joint tuberculosis, without demonstrable active tuberculous involvement in the lung, tubercle bacilli were found in the stomach juice in seven (31.8 per cent). This rather surprising finding was amplified by investigating the usefulness of this method in other extrapulmonary manifestations of this disease. These included tuberculous lymphadenitis, pleurisy with effusion, renal tuberculosis and lupus vulgaris. The results show that examination of the fasting gastric contents is of importance in establishing the diagnosis in a substantial percentage of such cases.

CONCLUSIONS

1. Bacteriological examination of the fasting gastric contents is an important, sensitive and reliable aid in the diagnosis of tuberculosis. It is a simple procedure which can be carried out by the physician, by a trained nurse, attendant or laboratory technician.

2. It is useful not only in pulmonary tuberculosis but also in extrapulmonary forms of this disease.

3. It is of value as a gauge in the clinical management of tuberculous patients in that, with its aid, one can ascertain the progress of the healing process in pulmonary cases

undergoing any form of medical or surgical treatment.

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Technical Aspects of Therapeutic Malaria*

LAWRENCE I. KAPLAN, M.D. and HILTON S. READ, M.D.

New York, New York

Atlantic City, New Jersey

THE technical aspects of induced malaria in the treatment of neurosyphilis have been inadequately appreciated, even in many institutions concerned with its use at the present time. Overburdened by the effort to provide sufficient neuropsychiatric care many of these hospitals have lacked the opportunities and facilities for studying the technical problems involved in this therapeutic procedure. Reliance upon the arbitrary, time-worn use of routine inocula of 5 to 10 cc. of infected blood, with lack of attention to immune mechanisms involved in the use of different malaria strains, among other things, has resulted in irregular, unpredictable infections, often difficult to evaluate with respect to therapeutic adequacy.

Success of penicillin in the treatment of neurosyphilis has by no means outmoded the usefulness of inoculation malaria in this disease. Reports of results following penicillin therapy alone^{1,2} certainly emphasize its value in this frequently crippling affliction, but certain types of neurosyphilis, notably those involving the parenchymatous central nervous system, will probably require a combination of induced malaria (as the most valuable form of fever therapy) and penicillin (as the most desirable chemotherapeutic agent). In the light of experience in the armed forces it therefore seems appropriate at this time to recount recent advances in the technical aspects of therapeutic malaria and their practical applications.

In the interval between July, 1944 and October, 1945, a total of more than 450 patients with neurosyphilis were treated with induced malaria at the Finney General

Hospital Neurosyphilis Center. Every clinical variety of neurosyphilis was encountered but the majority of cases were of the asymptomatic type in young, otherwise healthy, male adults. The course of therapeutic malaria and its complications could be readily evaluated, therefore, without the confusing introduction of neuropsychiatric symptomatology. Nine strains of plasmodia were utilized for inoculations. These consisted of five strains of *Plasmodium vivax*, four of which were recovered from individuals originally infected with the natural disease in the Southwest Pacific theatre, three strains of *Plasmodium malariae* and one strain of *Plasmodium falciparum*. Technics of inoculation included application of infected mosquitoes and the intravenous or intradermal inoculation of infected blood.

The technical advances in the use of therapeutic malaria can be roughly divided into three phases, each of which will be considered separately, as follows:

QUANTITATIVE PARASITE COUNT

Estimation of the density of malaria parasites in the blood of an infected individual has contributed greatly to better understanding of the characteristics of both natural and induced malarial infections. With the aid of this laboratory procedure, the immune response can be more precisely recognized and classified, and the technics of blood inoculation for inducing the therapeutic disease can be placed on a predictable, quantitative basis.

Technic. The technic of the quantitative parasite count, Boyd's modification of that described by Earle and Percz³ may be de-

* Investigations reported in this paper were carried out at the Army's Neurosyphilis Center, Finney General Hospital, Thomasville, Ga., in collaboration with Mark F. Boyd, M.D., Director of the Station for Malaria Research (Rockefeller Foundation) Tallahassee, Fla., and Frederic T. Becker, M.D., former Chief of Dermatology and Syphilology Section, Finney General Hospital.

scribed as follows: The materials required are (1) capillary pipettes graduated to deliver 5.0 c. mm. of blood; (2) glass slides on which are ruled or etched rectangles measuring 3.0 by 15.0 mm.; (3) a microscope, the ocular of which contains a Howard disc micrometer, the surface of which is ruled with one large square, divided into sixteen minor squares and so calibrated that with a predetermined tube length the area on a slide covered by the large square on the micrometer is known; (4) diluted Giemsa's stain.

The method used is as follows: (1) Discharge exactly 5.0 c. mm. of blood onto the ruled rectangle of the slide carefully avoiding bubbles. With a needle point carefully spread the blood out to the edges and into the corners of the ruled area. Allow it to stand in a horizontal position until dry. Since 5.0 c. mm. of blood are spread over 45 sq. mm., there will be spread over each sq. mm. of the rectangle 0.11 c. mm., or $\frac{1}{9}$ c. mm. of blood. (2) Stain smear in Giemsa's stain as any other thick smear; wash, drain and dry. (3) If it is assumed that calibration of the micrometer disc has shown that the outline of the large square covers 0.01 of a sq. mm. on a slide when the stained smear is placed under the microscope, it will be necessary to count the parasites observed in one hundred consecutive and discrete fields to obtain a sample of the parasites in the blood spread over 1.0 sq. mm. The fields should be selected while the smear is transversed on different parallel lines. The total of the parasites counted in one hundred fields will, when multiplied by nine, give the number/cu. mm. (Fig. 1.)

Classification and Management of Immune Responses. Normal variations in the parasite density for malaria infections differ with the species of plasmodia encountered. Vivax parasitemias usually average 20 to 40,000 parasites per c. mm. at the height of activity and rarely exceed 50,000 per c. mm. Quartan (*P. malariae*) parasitemias, involving chiefly the aged erythrocytes, rarely reach a height of 20,000 per c. mm. and usually remain

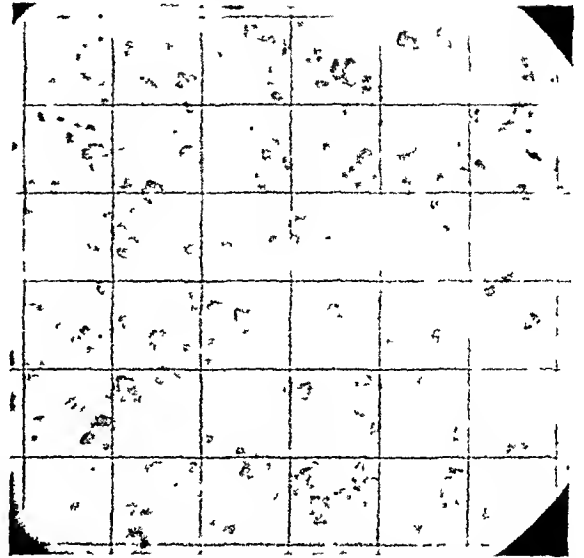


FIG. 1. Photomicrograph (95X) of thick smear, showing malaria parasites in relation to the squares of the Howard disc.

below 10,000 per c. mm. There is no established limit to falciparum parasitemias but the danger line averages between 100 and 200,000 parasites per c. mm. If a falciparum parasitemia exceeds 500,000, a fatality is almost inevitable unless prompt, repeated phlebotomies and transfusions are successfully instituted.

Correlation of hourly temperature records and quantitative daily parasite counts in a series of 300 cases of neurosyphilis (225 white and 75 negro patients) treated with therapeutic malaria has demonstrated four main types of immunologic reactions:⁴ (1) hyperimmune; (2) immune; (3) partially immune; (4) hypersusceptible.

In the hyperimmune response, rarely encountered in therapeutic malaria, neither temperature elevation nor demonstrable parasitemia follows inoculation of massive doses of trophozoites (50 to 100 million). Presumably these patients have had previous exposure to the same strain of malaria or have a marked racial immunity, both of a homologous type.

The immune reaction is characterized by development of a slight parasitemia following heavy inoculation, unaccompanied by any febrile response above 100°r. This was frequently encountered in negro soldiers inoculated with a vivax strain. When

it occurs in white patients, it usually serves as evidence that they have had previous exposure to a homologous strain of malaria.

The partially immune response (Fig. 2) has been a provoking problem in therapeutic malaria. It initiated the cross inocu-

the patient has had previous experience with a heterologous strain of malaria and will not complete a successful treatment course with the single inoculation. Those who in spite of thorough interrogation evade pre-inoculation recognition should be dis-

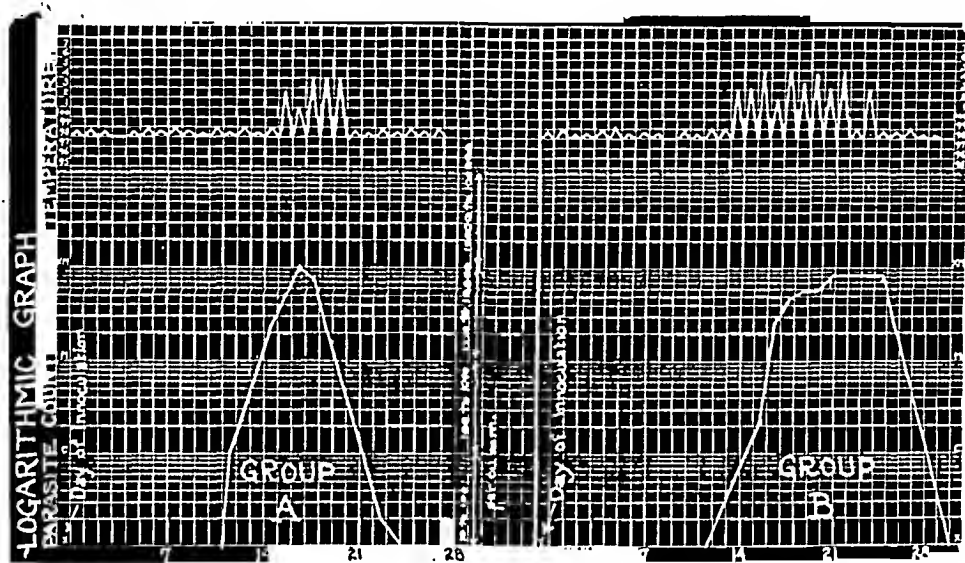


FIG. 2. The partially-immune response, Groups A and B, illustrating the relation of the parasite density to the febrile course.

lation immunity studies, an effort to find practical means of completing therapeutic malaria courses without prohibitively prolonged periods of hospitalization. This type of immune response can often be predicted by merely eliciting from the individual the history of a previous attack of natural malaria. However, a number of white patients with negative histories are still subject to a partially immune response.

In these cases following inoculation parasites will appear in the blood and slowly increase to a density of several hundred per c. mm. before the occurrence of any febrile response. The patient then experiences from three to seven paroxysms whereupon the parasite count drops precipitously and the patient becomes afebrile. Individuals developing partially immune responses may be divided into two groups: (A) Those experiencing less than five paroxysms of fever to 103°F. or more and (B) those experiencing five to eight such episodes. This type of reaction, particularly group B, indicates that

covered promptly postinoculation by the course of the parasitemia, and should be treated with a plasmodicidal drug and reinoculated with another strain or species of malaria.

The hypersusceptible patient (Fig. 3) will usually develop fever several days before parasites are microscopically discernible in the blood. With the parasitemia maintained at a high level, these individuals may experience a prolonged number of paroxysms unless interrupted by antimalarial therapy. These courses usually average sixteen to twenty-five paroxysms but a total of twenty-seven paroxysms was permitted in one of our patients, and Dr. Boyd has observed continuous clinical activity without a remission for ninety-five days.

Of the 300 patients studied for immune response in this series, 208 white and 8 negro patients received primary vivax inoculations. Of the white patients, twenty-three exhibited the partially immune type of response and required additional inocula-

tions. Three of the negroes had hyperimmune reactions, two immune reactions and three partially immune reactions. None of the negroes experienced susceptible courses with vivax malaria.

The daily parasite count was particularly helpful in following the quartan infections

White candidates from the United States who present a history of previous natural infection, individuals from the Mediterranean area or Puerto Rico and all negroes should be routinely inoculated with quartan malaria. Vivax malaria is the species of choice in all other white patients. Of those

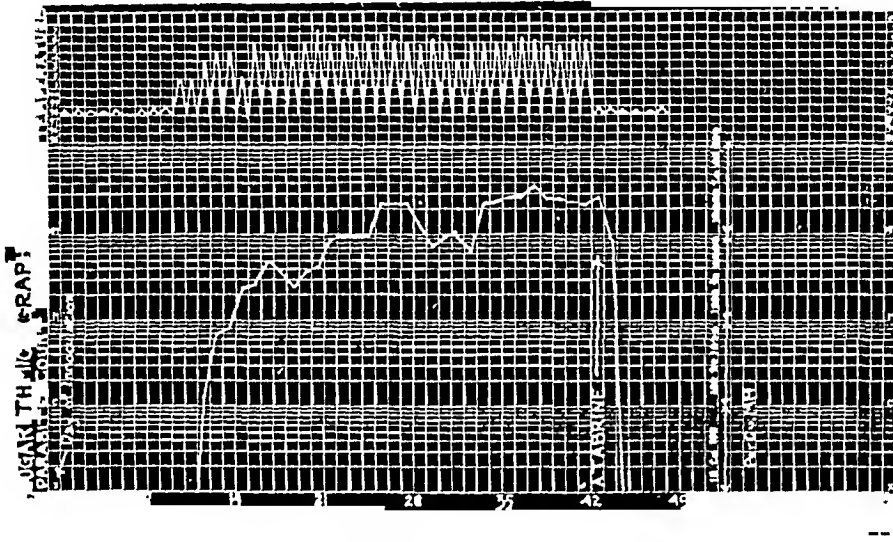


FIG. 3. The hypersusceptible response.

which were used routinely as the primary inoculation species in the remainder of the negro patients. The incubation period of quartan malaria following intravenous inoculation averages between twelve and fifteen days. A rising parasite level in the blood gives assurance that a febrile course will ensue. Parasitemia failing to exceed 3,000 per c. mm. thirty days following inoculation, with absence of any fever above 103°F. , is fairly good evidence that the patient has a relatively high degree of immunity and that some other form of therapy is indicated. The history was of no value in forecasting an immune reaction in the negro patients. In our series, seven of the negroes inoculated with quartan malaria did not complete susceptible courses and required additional fever therapy, two with falciparum malaria and four with hypertherm cabinet therapy.

These observations led to standardization of rules governing the inoculation of neurosyphilis patients with therapeutic malaria.

in this latter group who then experience a spontaneous remission prior to completion of therapy, those who have initially completed less than five paroxysms should be reinoculated with quartan malaria. Those who have experienced more than five paroxysms may be satisfactorily reinoculated with a heterologous strain of vivax malaria.

Quantitative Inoculations of Malaria Parasites. In addition to its use in permitting the early recognition of exuberant or runaway infections and early forecast of immune types of reaction which require termination of a morbidity-producing but therapeutically unsatisfactory parasitemia, the quantitative parasite count establishes more precise control over the methods of malaria inoculation and the subsequent febrile courses.⁵

It is becoming well recognized that the majority of vivax infections, either naturally or artificially induced, exhibit quotidian cycles with varying degrees of irregularity

rather than the commonly described pure tertian cycle. Following either mosquito inoculation or use of inocula of 5 to 10 cc. of infected blood without reference to parasite density, a number of days of remittent fever, characterized by continuous low grade temperature elevations of 101 to 103°F. and accompanied by severe malaise and exhaustion, is experienced. This irregular febrile course frequently debilitates patients prior to the establishment of true malaria paroxysms which are considered to be the essential feature of the therapeutic disease.

This initial period of remittent fever is probably the result of asynchronization of different broods of malaria parasites, apparently produced by the injection of large numbers of organisms in different stages of schizogony. Synchronization of broods occurring only after several days of clinical activity permits domination by a single brood and cycle. If a single parasite could be injected into the blood stream, only one brood of parasites would mature and only one cycle of paroxysms, typically tertian, presumably would ensue. Inoculation of single trophozoites has been accomplished successfully by the use of a micropipette at the Station for Malaria Research, Tallahassee, Florida, but the technic is time-consuming, requires the utmost skill and cannot yet practicably be applied clinically. However, in an effort to reduce remittent fever to a minimum, we have employed the quantitative parasite count in a technic of inoculation based on predetermined parasite doses low enough either to suppress or completely to eliminate this disturbing period of fever in most patients.

In this study duration of the period of remittent fever and the type of subsequent febrile cycle were analyzed in a series of 205 white patients who experienced susceptible reactions to inoculation with vivax malaria. The susceptible response was a necessary prerequisite since it was discovered earlier that the type of cycle and the intensity of remittent fever were dependent not alone on the technic of inoculation

but also on the degree of malaria immunity of the individual patient. The technics of inoculation used in this investigation included: mosquito inoculation with a minimum of two infected mosquitoes applied per patient; intradermal inoculation with a

TABLE I
SUMMARY OF DATA

Method of Inoculation	No. Patients Inoculated	% with Tertian Cycles	Distribution of Patients (%) by Period (days) of Remittent Fever					
			0	1	2	3	4	5
Intradermal.	26	57.8	42.3	23.1	11.5	19.3	0.0	3.8
Mosquito.	58	22.4	8.6	17.2	12.1	32.8	15.5	13.8
Intravenous (1-5 m).	56	37.5	23.2	17.8	17.8	17.8	16.2	7.2
Intravenous (6-25 m).	29	31.0	13.8	10.3	31.0	24.1	13.8	7.0
Intravenous (26-150 m).	36	25.0	11.1	11.1	22.2	13.9	19.5	22.2
Intravenous (1 m).	28	42.9	35.7	17.9	14.3	14.3	14.3	3.5
Intravenous (2-5 m).	28	32.1	10.7	17.9	21.4	21.4	17.9	10.7

total of 0.2 cc. of blood averaging a parasite count of 5,000 per c. mm. (total dose, 1 to 2 million parasites intracutaneously); and intravenous inoculation with total doses varying from 1 to 150 million parasites, determined by using graded inocula of 0.05 to 10.0 cc. of blood with different parasite densities. The quantitative parasite dose of donor's blood was determined in the following manner: quantitative parasite count of donor's blood = 5,000/c. mm.; inoculum of 1.0 cc. = 5 million parasites; inoculum of 0.2 cc. = 1 million parasites; inoculum of 10.0 cc. = 50 million parasites.

Table I summarizes the information obtained in this survey, indicating the number of patients inoculated by each technic, the type of subsequent febrile cycle and the percentages of patients by group, experiencing periods of remittent fever lasting zero, one, two, three, four or five days. The intravenous parasite doses were grouped for convenience into 1 to 5 million (further subdivided into 1 million and 2 to 5 million groups), 6 to 25 million and 26 to 150 million parasites.

Mosquito inoculation and intravenous inoculation with 26 to 150 million parasites produced the greatest number of long

periods of remittent fever. On the other hand, intradermal inoculation was followed by the least severe period of remittent fever, with 76.9 per cent of patients experiencing it for two days or less and 42.3 per cent not at all. However, the occurrence of 18.8 per cent (6 patients) unsuccessful "takes" as a result of technical difficulties excludes this method from routine clinical use.

Intravenous inoculations revealed that in susceptible patients the higher the parasite dose the longer the period of remittent fever in the greatest percentage of cases. The lower the parasite dose, the shorter and less severe is the remittent fever and the more closely does it resemble the results obtained following intradermal inoculation. Since total parasite doses of less than 1 million often require laborious dilution methods which appreciably diminish the clinical applicability of the technic, and since the 1 million parasite dose produces the most satisfactory reduction in remittent fever following intravenous inoculation (invariably resulting in successful "takes,") it is recommended as the standard inoculation procedure in vivax malaria therapy of neurosyphilis in susceptible white patients. The 1 million parasite dose eliminated the period of remittent fever in 35.7 per cent of patients and diminished it to two days or less in 67.9 per cent of patients in this study. In addition the greatest percentage of tertian cycles after intravenous inoculation followed the use of this parasite dose.

In brief summary then, the quantitative parasite count, a relatively simple laboratory procedure, can be of inestimable aid in determining the severity of a malaria infection and degree of the patient's resistance, in forecasting an immune response requiring intervention and retreatment, and in rather precisely regulating the febrile course by facilitating predetermined quantitative inoculations.

HETEROLOGOUS STRAINS OF PLASMODIUM VIVAX

Management of patients who experience partially immune types of reaction (group

B, five to eight paroxysms) following inoculation with *P. vivax* has been simplified by the controlled use of heterologous strains of this species of malaria. Demonstration of the characteristics of homologous and heterologous strain immunity by the use of strains of *P. vivax* differing in geographic origin has provided an effective tool for completing therapeutic malaria courses in this partially immune group without requiring reinoculation with quartan malaria. The hazard of accidental transfusion malaria as a result of the prolonged latency of quartan infections, reportedly thirty years or more in some instances, and the prolonged hospitalization and morbidity occasioned by the lengthy incubation period and longer duration and cycle of paroxysms in these infections have raised justifiable objections to the use of this species in reinoculations.

Cross Inoculation Technic. The difference between substrains of the same species of malaria is best illustrated by the technic of cross inoculation,⁶ whereby a heterologous strain produces definite clinical activity following the reinoculation of a patient who had previously experienced clinical activity with another strain. Five strains of *P. vivax* were utilized in our study of this strain difference. Strain M (Pv. McCoy) is the primary endemic strain of Southeastern United States, having been originally recovered in the Florida-Alabama area. Strains A, B, C and D were recovered from soldiers originally infected in the Southwest Pacific Islands of Guadalcanal, New Guinea and Bougainville.

Twenty-seven patients were completely studied by the technic of cross inoculation. In most instances the original vivax inoculation was performed intravenously, but a few successful mosquito and intradermal inoculations were also employed. Clinical activity following the original inoculation persisted until the occurrence of a spontaneous remission. No therapeutically interrupted original infections were included because of the greater possibility of active recurrence of the original strain later in the patient's

hospitalization. In spite of the negative histories of previous malaria attacks in twelve of the twenty-seven patients, most of them had some degree of malaria immunity at the onset with spontaneous remissions occurring prior to the exhaustion of the patient by a prolonged number of paroxysms. Reinoeculation and further clinical activity was thus feasible within the therapeutic realm.

After the first spontaneous remission, quinine therapy (10 gr. per 50 pounds of body weight daily for five days) was withheld until the parasitemia decreased to submicroscopic densities. This was merely an added precaution in sterilizing the blood stream prior to reinoeculation. Three to five days following completion of quinine therapy, an adequate interval for excretion of the drug, reinoeculations with either homologous or heterologous vivax strains were accomplished intravenously. Following the reinoeculation, clinical activity ensued until the development of a second spontaneous remission. Routine atabrine therapy was withheld until the second parasitemia was either negative or at insignificant levels at the end of two weeks following the last bout of clinical activity.

Reinfection Index. Since interest was primarily directed to the relationship of different vivax strains to each other and not to the varied individual immunity of patients prior to original inoculation, it became necessary to determine some factor which would largely cancel the effect of previous immunity on interpretation of the results of cross inoculation. The factor was designated the reinfection index, and was calculated in each case by considering the number of paroxysms experienced after reinfection as a percentage of the number of paroxysms experienced after original infection. For example, in the case of a patient developing eighteen paroxysms on original infection and two on reinfection, the index would be 11.1. On the other hand, in the case of a patient experiencing four paroxysms on original infection and two on reinfection, the index would be 50.0 in spite

of an identical number of paroxysms following reinoeculation. Previous individual immunity is thus largely eliminated from the analysis, and the higher the reinfection index the greater is the difference between the strains cross inoculated.

TABLE II
SUMMARY OF MEAN VALUES

Patients Reinfected with Homologous Strains (5):	
Duration of paroxysms following original infection.....	10.2
Duration of paroxysms following reinfection....	1.0
Reinfection index.....	10.5
Patients Reinfected with Heterologous Strains (22):	
Duration of paroxysms following original infection.....	7.5
Duration of paroxysms following reinfection...	4.5
Reinfection index.....	74.3
Individual Heterologous Reinfection Indices of Each Strain:	
M vs A, B, C, D.....	73.1
A vs M, B, C, D.....	78.8
B vs M, A, C, D.....	62.6
C vs M, A, B, D.....	70.0
D vs M, A, B, C.....	86.1

Heterologous Immunity. Table II lists the mean values of the results obtained in this cross inoculation study. It is apparent that heterologous immunity exists when reinfection of a patient with a strain of *P. vivax* differing in geographic origin from the original strain results in definite clinical activity sufficient for the completion of an interrupted course of therapeutic malaria. In this series of cases duration of the heterologous reinfection averaged 74.3 per cent (reinfection index) of the duration of the original infection, adequate activity for the completion of a course of treatment following a partially immune response with five or more paroxysms. Conversely, homologous immunity is characterized by the production of minimal clinical activity in patients reinfected with the same or similar substrain of vivax malaria. Duration of the homologous reinfection in this series averaged 10.5 per cent (reinfection index) of the duration of the original infection with that same strain, indicating clearly the futility of employing homologous strains as secondary agents for the completion of malaria therapy. From these observations, and from the recognized undesirability of reinoculat-

ing patients with quartan malaria when this is not necessary, heterologous strains of *P. vivax* are recommended for the re-inoculation of white patients with neurosyphilis who experience group B partially immune types of original infection.

TEMPORARY DRUG INHIBITION OF THERAPEUTIC MALARIA

The frequent irregularity of therapeutic malaria infections has resulted in investigations designed to determine the value of various antimalarial agents in regulating or temporarily interrupting malaria paroxysms without permanent termination of the infections. Small doses of quinine, sulfonamides, arsenicals and intravenous 20 per cent dextrose solution have all been used from time to time, but were unsatisfactory chiefly because of their unpredictability in a given infection.

In 1939, Schwartz⁷ first introduced sodium bismuth thioglycollate (thiobismol) as the most effective agent for reducing the frequency of paroxysms without completely eliminating them in vivax malaria. This work was confirmed by Brunsting and Love⁸ and by Young, McLendon and Smarr,⁹ who demonstrated quite clearly that thiobismol in 0.1 and 0.2 Gm. amounts had an inhibitory effect against half-grown vivax parasites. Paroxysms were frequently converted from quotidian to tertian periodicity, and usually remained tertian for the duration of the infection and often through several subsequent inoculations. The drug permitted a full course of therapy without causing exhaustion from daily febrile paroxysms, and also facilitated temporary interruptions when these were indicated by minor complications. Thiobismol had been employed similarly in quartan malaria but no consistent results, other than occasional unpredictable interruptions, could be obtained by these investigators.

A further study of the use of this drug in quartan malaria¹⁰ was begun on our service when the accidental elimination of apparently half-grown *P. malariae* parasites followed administration of the drug to

patients experiencing mixed vivax and quartan infections. A total of fifty-six injections of thiobismol, in doses of 0.1 and 0.2 Gm., were then administered intramuscularly at different intervals to thirty-eight patients experiencing true quartan (one paroxysm every three days), double quartan (two paroxysms every three days) and quotidian quartan (three paroxysms every three days) types of therapeutic malaria. Chance distribution of injections during the period of seventy-two hours from the onset of the main quartan paroxysm was permitted. Results of this investigation are presented in tabular form in Table III. For simplification of description the paroxysms occurring in true quartan cycle are referred to as the A paroxysms. Subsequent intermediate paroxysms occurring on the second or third day following the main cycle have been termed the B and C paroxysms respectively, and contribute in various combinations to the irregular double or quotidian quartan cycles. The parasite broods maturing during the respective paroxysms are similarly designated the A, B, and C broods. From the table it is noted that four types of cycles were encountered: A (true quartan), AB and CA (double quartan) and ABC (quotidian quartan). Those paroxysms remaining unaffected or which were specifically removed by injections of thiobismol are appropriately recorded in the table.

Eighty-seven and five-tenths per cent of the injections administered to patients with double quartan or quotidian quartan malaria resulted in temporary interruption and/or reduction in frequency of paroxysms. Partially grown parasites were uniformly affected in these cases, and no mature or very immature (less than one-third grown) parasites were influenced by the drug. Only 42.5 per cent of the injections given to patients having true quartan malaria was followed by temporary interruption. However, in all of these patients showing definite clinical effects only partially grown parasites (one-third, one-half or two-thirds grown) were inhibited. None of the five

TABLE III
CLINICAL EFFECTS OF THIOMBISOL ON QUARTAN MALARIA RELATED TO THE TIME OF ADMINISTRATION, AGE OF PARASITE BROODS AND PREVIOUS CYCLES

Time of Administration	Age of Broods			True Quartan A			AB		Double Quartan			Quotidian Quartan ABC			
	A	B	C	Re-moved	Inter-ruption No Effect*	No Effect*	Total	A Re-moved	B Re-moved	Total	A Re-moved	B Re-moved	B and C Re-moved	No Effect	Total
±6	Mat.	$\frac{2}{3}$	$\frac{1}{3}$..	5	6	11	..	4	4	1	..	1
7-8	$\frac{1}{6}$	$\frac{5}{6}$	$\frac{1}{2}$..	1	..	1	1
19-30	$\frac{1}{3}$	Mat.	$\frac{2}{3}$	2	6	8	16	1	..	1	2	22
31-42	$\frac{1}{2}$	$\frac{1}{6}$	$\frac{5}{6}$	2	..	2	4	1	5
43-54	$\frac{2}{3}$	$\frac{1}{3}$	Mat.	1	..	5	6	2	1	9
55-66	$\frac{5}{6}$	$\frac{1}{2}$	$\frac{1}{6}$	2	2	1	3
Total				5	12	23	40	1	4	5	2	1	1	2	56

* Interruption for four to eight days, with reappearance of the A cycle.

† Prolonged interruption for sixteen to thirty days after injection.

‡ Calculated as the number of hours from the onset of the main A paroxysm.

§ Listed as fractions of maturity, i.e., one-half equals half-grown parasites.

patients with original parasite densities above 10,000 parasites per cm. responded to thiobismol injections with definite clinical effects. Thus thiobismol appears to be an effective agent for reducing the frequency of paroxysms and regulating the febrile cycle in patients experiencing double quartan or quotidian quartan malaria with the usual parasite densities below 10,000 parasites per c. mm. This drug can, therefore, be equally useful in both vivax and quartan malaria infections, enabling neurosyphilis patients better to tolerate complete courses of therapy.

SUMMARY

1. Technical refinements of the treatment of neurosyphilis with induced malaria have long been overlooked. An appreciation of these aspects of treatment will lead to a sound clinical approach to the problem, to an understanding of the immune mechanisms involved, and to the wider adoption of techniques which are relatively simple and which aid in the production of satisfactory courses of the disease.

2. The quantitative parasite count eliminates confusion and waste of time in the use of therapeutic malaria by materially aiding in determining the severity of a given malaria infection and the degree of the patient's resistance, in rapidly forecasting an immune response requiring intervention and retreatment without wasteful weeks or months of observation, and in the rather precise regulation of the febrile course by facilitating quantitative inoculations.

3. Heterologous strains of *P. vivax* have been shown to produce sufficient clinical activity in previously vivax-infected individuals to allow their routine use for the reinoculation of white neurosyphilis patients experiencing partially immune types of original infection (five to eight paroxysms) thus eliminating the undesirable use of quartan strains for reinfection.

4. Criteria for malaria inoculations in the treatment of neurosyphilis have been established: (1) White patients with a history of malaria, individuals from the Mediter-

ranean area, Puerto Rico, or highly endemic malaria zones, and all negroes should be primarily inoculated with quartan malaria, intravenously in large doses (more than 10 million parasites). (2) All other white patients without a history of malaria should be primarily inoculated with vivax malaria, intravenously in doses of 1 million parasites. (3) Patients in group B who develop partially immune responses with less than five paroxysms should be reinoculated with quartan malaria. (4) Patients in group B who develop partially immune responses with five paroxysms or more should be reinoculated with heterologous strains of vivax malaria.

5. Sodium bismuth thioglycollate (thio-bismol), which inhibits partially grown parasites, can be employed to regulate both vivax and quartan infections when irregular cycles occur.

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441 E. 20 St. 5407 Atlantic Ave.

Left Vocal Cord Paralysis Associated with Cardiac Disease*

DAVID A. DOLOWITZ, M.D. and C. S. LEWIS, M.D.

Salt Lake City, Utah

PARALYSIS of the left recurrent laryngeal nerve has been observed occasionally in association with cardiac enlargement, but a causal relationship is still questioned by many.¹ Those who believe that such a relationship exists are, in the main, unable to agree on the exact mechanism involved. This paper adds two cases of the syndrome to those which have been reported. Anatomic studies of the recurrent laryngeal nerve were also made in twenty-five cadavers. From these studies a plausible hypothesis is presented for consideration. It is based on anatomic evidence which may elucidate this unusual syndrome.

The first examples of vocal cord paralysis in heart disease were described by Ortnier² in 1897 when he reported two cases of mitral stenosis with left vocal cord palsy. The autopsies confirmed the diagnosis of mitral stenosis. In the first case the left recurrent nerve was caught between the left atrium and the left bronchus and in the second instance between the left atrium and the aortic arch.

In 1911, Fetterolf and Norris³ collected thirty-seven cases from the literature and added one of their own. In reviewing these cases, and in reporting their own anatomic study, they concluded that (1) the nerve must be "squeezed" between the left pulmonary artery and the aortic arch or the ligamentum arteriosum and (2) any factor causing dilatation or upward displacement of the left atrium, the left pulmonary vein or the left pulmonary artery would tend to cause impingement on the nerve. In disagreement with Ortnier these authors emphasized that it would be impos-

sible for the atrium to press directly on the aorta or bronchus, pinching the nerve. They pointed out that some of the cases reported as mitral stenosis were complicated by inflammatory conditions. Pericardial effusion, pericarditis, aneurysm of the aorta or the pulmonary artery, or enlarged peribronchial lymph nodes may have caused pressure on the nerve resulting in paralysis. Fetterolf and Norris cast doubt on an explanation previously advanced by Kraus⁴ in which he claimed that the nerve was paralyzed by being pulled down by the aortic arch. The traction is due to an enlarged right ventricle.

In 1934 King, Hitzig and Fishberg⁵ presented three cases of arteriosclerotic heart disease with left ventricular failure (two of which were complicated by myocardial infarction) in which left vocal cord paralysis was present. They assumed that the palsy was caused by compression of the nerve between the left pulmonary artery, the aorta and the ligamentum arteriosum. Their explanation differs from that of others by the stress placed upon dynamic dilatation of the pulmonary vessels as an important factor in causing compression of the nerve. They pointed out that this may be revealed by radiosopic examination but might not be detected at autopsy.

Erlanger and Levine⁶ presented two cases of congenital atrial septal defect with recurrent laryngeal nerve palsy and cited five other cases of congenital heart disease accompanied by hoarseness, one of which was an example of the so-called Lutembacher's syndrome (mitral stenosis plus atrial septal defect). In all the cases con-

* From the Departments of Medicine and Surgery, University of Utah School of Medicine, Salt Lake City, Utah.

spicuous enlargement of the pulmonary artery was present. The nerve palsy in these cases, the authors concluded, was best explained by the mechanism proposed by Fetterolf and Norris.³

Notkin⁷ agreed with the explanation of Fetterolf and Norris and of King, Hitzig and Fishberg⁵ but suggested in addition that thrombi in the auricle, thrombosis of the pulmonary artery, atheromas and sclerosis of the pulmonary artery may become contributory factors. It was presumed by these authors that the focal induration produced by these lesions exerts more effective pressure than soft tissue. This explanation was supported by Price⁸ and Wallerstein.⁹

Arguments against a causal relationship between cardiac disease and left recurrent laryngeal nerve palsy are chiefly based on the fact that while mitral stenosis is a rather common condition, associated left vocal cord paralysis is quite rare. Smith, Lambert and Wallace¹⁰ reported 235 cases of paralysis of the recurrent laryngeal nerve. Only five of these cases were associated with heart disease; an additional thirty-four were accompanied by aneurysm of the aorta. Reiche¹¹ reviewed 300 cases of mitral stenosis and found left recurrent laryngeal palsy in only two instances. Scheifley and Smith¹ reviewed 223 cases of left laryngeal palsy and found mitral stenosis as the presumable causative agent in ten cases. They pointed out, however, that in 51 per cent of their cases no cause for the paralysis was found. Scheifley and Smith assumed that heart disease may have been present in some cases in this group. They found that while the incidence of mitral stenosis in a general clinic population (Mayo) was 0.5 per cent, this type of heart disease was present in 5.0 per cent of 223 patients with left recurrent laryngeal nerve palsy. Therefore, it was noted that mitral stenosis was ten times as frequent in cases of left recurrent laryngeal nerve palsy as in a control group. In another group of patients with right cord paralysis no cases of mitral stenosis were found.

Apparently the causal relationship be-

tween cardiac enlargement and recurrent nerve palsy is not established conclusively. If a causal relationship does exist, the mechanism is not fully understood. The two following instances of the syndrome are being reported to add to the available data on this condition:

CASE REPORTS

CASE I. C. R. (8855), a twenty-five year old single, white male entered the Salt Lake General Hospital on February 19, 1946, because of severe congestive heart failure. About one month prior to admission the patient had contracted a febrile illness characterized by cough, fever, general malaise, dyspnea, orthopnea, a sense of epigastric pressure and fatigue. The cough, fever and malaise disappeared after two weeks but symptoms of cardiac embarrassment progressed. About four days prior to admission the patient noted edema of the feet and legs. At that time he was unable to sleep for more than thirty minutes at a time. The history revealed symptoms suggestive of acute attacks of rheumatic fever at the ages of eight and twelve years. He then enjoyed a normal life with usual activity until four years prior to admission when he began to restrict his activities because of dyspnea on exertion and a feeling of abdominal fullness. The family history was not contributory.

On physical examination the patient appeared markedly dyspneic and orthopneic, and displayed slight cyanosis of the lips and nail beds. Minimal clubbing of the fingers was noted. The neck veins showed systolic pulsation. Percussion of the chest revealed dullness over the right base posteriorly with markedly diminished breath and voice sounds over this area. Moist râles were heard at both lung bases posteriorly. On percussion the heart was enlarged to the left anterior axillary line and the point of maximum impulse was located in the sixth intercostal space in the left anterior axillary line. The rhythm was regular. A systolic murmur was heard over the apex and this was transmitted to the axilla. A low pitched diastolic rumble, which was localized in the apical region, and a high pitched early diastolic murmur were audible over the aortic area. The abdomen was somewhat distended and a fluid wave and shifting dullness were demonstrable. The edge of the liver which was firm and smooth was palpated 7 cm. below the right costal margin. There was

pitting edema of the lower extremities extending to the thighs. The temperature was 98.4°F., the pulse 78 and the respirations 22. The blood pressure was 130 systolic and 85 diastolic.

All the laboratory findings were within the normal range except for measurements of venous pressure (265 mm. of saline) and circulation time (decholin, 37 seconds). Vital capacity was 67 per cent of normal. Blood urea nitrogen was 32 mg. per cent on admission and 22 mg. per cent one week later. Urine was normal.

A roentgenogram of the chest revealed congestion of the lung fields with elevation of the right leaf of the diaphragm. The heart was enlarged in all diameters with the apex at the seventh rib anteriorly. There was marked prominence of the right cardiac border, the left atrial segment and the left pulmonary artery.

The electrocardiogram showed right axis deviation with very large P waves in leads I and II and U-shaped depression of the ST segment with inversion of T in leads II and III. The tracing was thought to be indicative of right ventricular and left atrial enlargement. The changes in the ST segment were assumed to be due to digitalis therapy. A clinical diagnosis of rheumatic heart disease with involvement of the mitral and aortic valves was made.

The patient improved following treatment with bed rest, diuretics, low sodium diet and digitalis. On the second hospital day the patient was noted to be slightly hoarse. Examination of the throat was negative but the hoarseness persisted. On the sixth hospital day, at a time when by clinical and roentgenographic examination the heart was decreasing in size, laryngoscopic examination revealed sluggish movement of the left vocal cord. On the eighth hospital day the left cord was completely paralyzed. As the patient improved the heart continued to decrease in size. The voice improved to a certain extent. The left cord, however, remained in cadaveric position and the right cord gradually crossed the midline to meet it. This condition has remained constant during the six months that the patient has been observed although the fixed left cord is gradually shifting toward a midline position with accompanying vocal improvement.

CASE II. R. B. (8696), a thirty-four year old housewife, entered the Salt Lake General Hospital on March 19, 1946, because of shortness of breath, difficulty in breathing while lying down and swelling of the ankles. These

difficulties had been present for four months and had become progressively more severe. Orthopnea and dependent edema soon developed. The patient was told that she had heart trouble at the age of seven years. She was kept out of school for one year because of "leakage of the heart." However, she married and went through three successive pregnancies without apparent difficulties. Two and one-half years before admission, following birth of her third child, the patient had an attack of the "flu" and was kept in bed. Hoarseness was first noted at that time and has persisted ever since. Her private physician examined the larynx and reported paralysis of the left vocal cord. About a year before admission the hoarseness improved to a point at which she could teach Sunday school. Since the onset of the present illness, the hoarseness recurred. The family history was not contributory.

Physical examination revealed a well proportioned white woman who spoke in a hoarse whisper. She was dyspneic, slightly cyanotic and presented a distinct malar flush. The chest was clear except for a few moist râles in both lungs posteriorly. Mild emphysema was present. The heart was enlarged to the left anterior axillary line and the point of maximum impulse was located in the fifth intercostal space. A harsh, high pitched systolic murmur was heard at the apex and along the left sternal border. The second aortic sound was louder than the second pulmonic sound. The rhythm was regular. The abdomen was somewhat distended and a fluid wave was present. The liver was enlarged to 8 cm. below the right costal margin, its edge being firm and smooth. Marked pitting edema of the ankles was present. Laryngoscopic examination revealed paralysis of the left vocal cord which remained in the cadaveric position of phonation. The right vocal cord did not cross the midline. The temperature was 98.6°F., the pulse 80 and the respirations 24. The blood pressure was 130 systolic and 70 diastolic.

The red blood cell count was 4.3 million per cu. mm., the hemoglobin was 12.3 Gm. and the volume of packed red cells was 39 cc. per 100 cc. of blood. The erythrocyte sedimentation rate was normal. The white blood cell count was 6,900 per cu. mm. and the differential count was normal. The Kahn test of the blood was negative; the venous pressure was 190 mm. of saline and the circulation time (decholin) was 25 seconds. The urine was normal. The blood uric

nitrogen was 15.5 mg. per cent and the total blood protein was 6.1 Gm. per cent, with 4.2 Gm. albumin and 1.9 Gm. globulin.

Roentgenographic examination of the chest revealed generalized enlargement of the cardiac silhouette. The apex of the heart lay in the eighth interspace. The right border of the heart extended far to the right of the midline. These findings were interpreted as indicating the presence of marked right atrial enlargement, right ventricular enlargement and some left ventricular enlargement. The aortic shadow was not visualized. The shadow of the pulmonary artery was very prominent. The pulmonary arteries were extremely dilated, and their finer ramifications extended out to the periphery of the lung field. The superior vena cava was visualized. In the right anterior oblique view the cardiac silhouette was seen to occupy practically the entire mediastinum, displacing the esophagus posteriorly. The barium-filled esophagus showed a marked indentation in the region of the pulmonary artery but no compression, suggesting left atrial enlargement. No aortic shadow could be seen. Fluoroscopy confirmed these findings and in addition revealed a marked "hilar dance."

The electrocardiogram showed a normal sinus rhythm with normally shaped P waves. The QRS complexes appeared notched and slurred and measured 0.14 seconds in width. A deep S wave was present in lead I and serial precordial leads revealed late activation of the right ventricular epicardial surface. Right axis deviation was present. RT junction appeared depressed in leads II and III. The curve was interpreted as an example of right bundle branch block with right ventricular enlargement. No atrial enlargement could be demonstrated. The clinical impression was that of an atrial septal defect. The presence of an associated mitral stenosis was suspected but could not be substantiated.

As the patient improved following appropriate management, it was noted that the voice became stronger. The right cord was seen to cross the midline and approximate the left, which remained in the cadaveric position.

COMMENTS

These two cases present the triad of (1) an enlarged heart, (2) increased pressure in the pulmonary circuit with resultant enlargement of the pulmonary conus and the

right ventricle and (3) left recurrent nerve palsy. The first patient was thought to have rheumatic involvement of the mitral and aortic valve with marked enlargement of the left atrium. The second patient was thought to have an atrial septal defect, possibly with mitral stenosis (Lutembacher's syndrome) and an enormous increase in the size of the pulmonary conus.

In reviewing the literature one is impressed by the fact that while left recurrent laryngeal palsy associated with heart disease is uncommon, the combination occurs too often to be merely coincidental. There has been much disagreement as to the mechanism by which an enlarged heart produces pressure on the recurrent laryngeal nerve. Too often a single factor has been proposed in explanation of all the cases. We believe that this view is not justified.

There seems to be no reason why a variety of anatomic lesions (mitral stenosis, arteriosclerotic heart disease with and without coronary occlusion, congenital heart disease and aneurysms of the large vessels) may not produce the syndrome. The left recurrent laryngeal nerve passes under the aorta in such a manner that it is in close approximation with the aorta, the ligamentum arteriosum and the pulmonary artery. These three structures form a triangle through which the nerve usually passes. In addition to dilatation or changes in position in any one of these structures their relationship may become altered by pressure exerted upon them, for example, by an enlarged left atrium. We are not in a position to say whether or not the left atrium can exert pressure directly on the nerve. We do believe, however, that changes in size or relationship of any one of a number of mediastinal structures is potentially capable of causing pressure on the recurrent laryngeal nerve. We believe that the explanation of Fetterolf and Norris³ is the most logical. These authors have assumed that the dilated heart transmits pressure through the pulmonary vessels, pressing the nerve against the aorta. Furthermore, back pressure in the pulmonary circuit with

resulting enlargement of the pulmonary vessels (King, Hitzig and Fishberg)⁶ seems to be compatible with this assumption.

It is interesting to speculate as to whether pressure alone, traction alone or both combined cause devitalization of the nerve and over how long a period this pressure must be applied. Judd, New and Mann,¹² working with dogs, found that pinching the nerve once "with a hemostat in a manner similar to that necessary to stop hemorrhage from a small vessel" will cause a temporary paralysis for thirty to ninety days depending on the anatomic point at which the nerve was pinched. The function of the nerve always returned. They also found that ligating the nerve with any type of suture material resulted in permanent paralysis. This would infer an inflammatory "ligature" about the nerve. When tissues as soft as the heart and great vessels are involved, it is hard to imagine a crushing injury so severe that the nerve could not recover. This view is strengthened by the findings in the first case in which the initial symptoms of paralysis appeared when the heart clinically and roentgenographically was decreasing in size. The voice change incurred while the heart was enlarged has not changed in over six months. The second case is of less help; although paralysis accompanied a bout of decompensation, exact x-ray studies were not made.

Despite the little attention paid Kraus's theory⁴ of tension traction causing the injury, it is hard to explain this away since aortic aneurysm remains the most frequent cause of paralysis in cardiac conditions. Further study is indicated.

Left laryngeal nerve palsy with cardiac enlargement is uncommon, and it must be assumed that in addition to the contributing factors listed certain inherent anatomic relationships between the structures of the mediastinum must be present before the nerve can be compressed. A potential space the size of a small lima bean exists in the critical triangle. It is possible that the degree of pressure, the length of time over which it is applied, and inflammatory changes in the

nerve may be contributory factors resulting in nerve paralysis. This view is strengthened by the first case in which paralysis occurred while the heart was shrinking in size and cardiac function was improving. Antecedent damage at the time when cardiac damage was maximal is thus suggested. Decreased compression of the nerve with reduction in the size of the heart while relieving the "compression" would not invalidate this hypothesis.

Careful anatomic study* of the area probably concerned in the production of this syndrome was made in five fresh and twenty-two fixed cadavers. In the area bounded by the aortic arch superiorly, the pulmonary artery inferiorly and the ligamentum arteriosum medially, one constantly finds a group of three to five lateral tracheobronchial lymph nodes. These nodes are always in close proximity to the left recurrent laryngeal nerve as it leaves the vagus nerve and loops around the aortic arch. They vary in size from 3 mm. in each dimension to 2 cm. by 1 cm. by $\frac{1}{2}$ cm.

In three of the cadavers studied one of these lateral tracheobronchial lymph nodes was firmly adherent to the vagus nerve. In one body, in addition to the larger node in contact with the vagus nerve, a smaller node was firmly anchored to the left recurrent laryngeal nerve immediately beyond its origin from the vagus nerve. (Fig. 1.) In this instance the left atrium and the pulmonary artery lymph node could conceivably compress the left recurrent laryngeal nerve against the aorta sufficiently to result in nerve fiber degeneration.

We believe that hypertrophy of a strategically placed lymph node can cause fixation of the left recurrent laryngeal nerve. This fixation could permit pressure on the nerve by either cardiac enlargement or pulmonary artery engorgement or both. These anatomic observations are considered so pertinent that additional studies are now under way.

*The anatomic studies were made by one of us (D. A. D.) under the direction of Dr. C. A. Swinyard, Professor of Anatomy, University of Utah.



FIG. 1. A view of the heart showing a lymph gland adherent to the left recurrent laryngeal nerve as it arches beneath the aorta. A, left recurrent laryngeal nerve; B, arch of aorta, C, lymph nodes, D, ductus arteriosus, E, left pulmonary artery; F, vagus.

Prognosis is good as to return of the voice. Some instances of vocal paralysis, with subsequent return of function of the affected cord, have been reported. Even in patients in whom there is permanent paralysis of a vocal cord the voice may recover to a variable extent. This improvement is due to compensation by the right cord which gradually crosses the midline to meet the left cord. Some of the cases that have complete voice return may have been due to intrinsic disease within the larynx and not to nerve palsy. This can best be illustrated by two cases of mitral stenosis seen by one of us (D. A. D.). In these cases the hoarseness was due to chronic laryngitis so severe as to impede the motion of both cords. Biopsy of the false cord confirmed the impression of intrinsic disease and with voice rest the condition gradually improved.

SUMMARY

1. Two examples of paralysis of the left recurrent nerve associated with heart failure

are reported. One patient developed this paralysis as a sequel to rheumatic heart disease with severe valvular lesions. The second patient developed hoarseness secondary to congenital deformity of the heart.

2. Many mechanisms have been proposed to explain the syndrome of left recurrent nerve palsy associated with cardiac disease. A review of these hypotheses shows that none fully explains the condition.

3. It appears from our anatomic studies that the lymph nodes in the triangle formed by the pulmonary artery, aortic arch and ligamentum arteriosum may effectively compress the left recurrent laryngeal nerve when accompanied by cardiac hypertrophy, pulmonary artery engorgement, or both.

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Parenteral Benadryl in Allergy*

SIDNEY FRIEDLAENDER, M. D. and ALEX S. FRIEDLAENDER, M. D.

Detroit, Michigan

WIDE clinical experience has demonstrated that oral administration of antihistamine drugs is frequently successful in temporarily alleviating symptoms in various allergic syndromes. The response to this form of medication varies greatly from one individual to another, depending to some extent on the site of allergic involvement as well as upon the intensity of symptoms. Certain types of allergic reactions, namely, those involving the skin, are more frequently controlled by these agents than are those in which the nasal and bronchial mucosa are the site of difficulty. It is of course possible that histamine plays a greater rôle in some allergic conditions than in others, or that the amount of histamine release in certain instances is too great to be controlled adequately by the usual non-toxic oral doses of the antihistamine drugs. There is also the consideration that the variable effect observed in similar cases may be related to differences in gastrointestinal absorption of the drugs. Occasionally, an increase in the amount of drug administered orally may be successful in controlling symptoms. When larger doses are used, however, side effects become more frequent and pronounced. For the usual ambulatory patient this side action limits the amount of drug that may be safely given. In the acutely ill patient the very common side effect of drowsiness is not a contraindication to the use of larger doses, and in severe allergic states sedation is often desirable. Very frequently, however, even large oral doses fail to produce symptomatic relief. In these cases parenteral administration of antihistamine drugs deserves consideration.

For some time we have had available for

clinical trial a solution of benadryl hydrochloride* containing 10 mg. per cc., suitable for parenteral administration. The action of this preparation was studied in twenty-five patients with severe allergic symptoms who either were not benefited by large oral doses of benadryl and other antihistamine drugs or to whom for some reason it was not practical to administer such medication orally. In most cases the drug was given intravenously but in some instances it was administered intramuscularly or subcutaneously. Urticaria and angioneurotic edema of a severe degree was present in fifteen patients. One of these was an infant of twelve months; the remainder were adults. Nine other patients were in "status asthmaticus" while one patient had severe migraine, allergic in nature.

Early in the use of this preparation it was learned that relatively small doses administered intravenously often produced a profound hypnotic effect. For this reason the initial injection in each case was carried out in the home or hospital. Ten mg. (1 cc.) of the drug was given slowly as the first intravenous dose and the effect observed. If relief of symptoms did not occur promptly and sedation was not marked, a second dose of 20 to 30 mg. (2 to 3 cc.) was repeated two hours later. In most cases 30 mg. intravenously exerted a marked sedative action lasting several hours and often induced sleep. In some instances 50 mg. (5 cc.) doses were necessary to produce this effect. While sedation appeared to be the most consistent effect of intravenous benadryl, very marked symptomatic relief occurred in certain patients who had not been favorably

* Benadryl hydrochloride supplied by Research Dept., Parke, Davis & Co., Detroit, Mich.

* From the Departments of Bacteriology and Medicine, Wayne University College of Medicine, Detroit, Mich

affected by considerably higher doses of the oral preparation.

The value of parenteral benadryl in urticaria was impressed upon us very early in this study by its dramatic effect in a man of forty-nine, seriously ill with generalized urticaria and angioneurotic edema of five weeks' duration. Large oral doses of benadryl as well as two other antihistamine drugs had failed to alleviate symptoms. The sudden onset of severe gastrointestinal hemorrhage further complicated the problem in this instance. Since morphine in repeated doses failed to control the restlessness and hematemesis, an initial dose of 10 mg. of benadryl was given intravenously. Only slight drowsiness occurred and a second dose of 30 mg. was given two hours later. Within a few moments the skin swellings noticeably diminished and the patient slept for the first time in several days. The same amount was repeated in three hours when the patient awakened complaining of pruritus. It was found necessary to administer 30 mg. at four-hour intervals during the next two days in order to control symptoms. Following the initial dose of benadryl, hematemesis ceased although stools remained tarry in nature for several days and occult blood was present for a week thereafter. With improvement of the patient's condition the effect of intramuscular and subcutaneous administration of benadryl was observed. Control of symptoms with less drowsiness occurred when given in this manner although slight local discomfort followed each injection. The patient preferred the subcutaneous to the intramuscular site and was able to administer the drug himself subcutaneously following discharge from the hospital. During the next two months, while under allergic study, he gave himself 10 to 20 mg. of the injectable benadryl once or twice daily to control urticarial symptoms. Repeated trial of oral antihistaminics continued to be without effect. No evidence of acute or chronic toxicity was noted during or after the prolonged use of the drug by injection.

Parenteral benadryl was found very help-

ful in twelve cases of severe "serum-sickness type" reaction following the use of penicillin. In contrast to many similar cases which are helped by oral administration of antihistamine drugs, the patients in this group failed to benefit from such medication during the acute stages of their difficulty. Benadryl given intravenously in doses of 10 to 30 mg. was usually effective in alleviating edema, pruritus and arthralgias for periods of four to twelve hours. Later in the course of these "serum-sickness type" reactions, when dermatographism appeared to be the principal remaining symptom, oral antihistaminics seemed to exert sufficient palliative action to warrant discontinuance of the intravenous material. A year old infant suffering from a severe penicillin reaction was benefitted remarkably by intramuscular injections of 5 to 10 mg. of benadryl every four to six hours over a period of a week. Despite the very marked palliative action it cannot be said at this time that the course of the penicillin reactions in these cases was perceptibly shortened by the intravenous use of the drug. In a severe case of acute urticaria due to aspirin, and in another case following a prophylactic dose of tetanus antitoxin in which no help was afforded by oral medication, control of symptoms was possible by the intravenous injection of benadryl.

Our experience with intravenous benadryl in nine cases of "status asthmaticus" indicates that its principal value in such patients lies in its sedative and hypnotic action. While reduction in the amount of asthma has been observed in some instances following the administration of 30 to 50 mg. intravenously, the effect has not been consistent enough on repeated administration to warrant its use to the exclusion of such valuable drugs as ephedrine, adrenalin, aminophyllin and iodides. In most cases, it has been of definite help through the production of a sedative effect so frequently desired in patients with severe asthma.

Intravenous benadryl was also used in a young woman with severe migraine of long standing in whom milk sensitivity was an important etiologic factor. During a par-

ticularly severe episode when usual measures, aside from opiates, were unsuccessful in relieving pain or inducing sleep, a 50 mg. dose of benadryl intravenously produced satisfactory sedation. This dose has been repeated on subsequent occasions during acute upsets with the same helpful effect.

Although comparatively little is yet known of the absorption, utilization and excretion of the antihistaminics, the potency of small intravenous doses suggests that only partial utilization of the drug may occur when given orally. It appears at this time that injectable benadryl should be used cautiously, and should be confined to those patients in whom it is reasonable to expect that antihistamine therapy would be of value and in whom the oral medication cannot be given or has proved ineffective. With these factors in mind, it often serves as

a helpful adjunct in the management of difficult cases. Present evidence indicates that antihistamine therapy, whether given orally or by injection, is a palliative and not a curative measure. The underlying allergic factors in each case must be carefully searched for and evaluated in order to determine the specific therapy necessary.

SUMMARY

A preparation of benadryl hydrochloride containing 10 mg. per cc., suitable for parenteral injection, was found beneficial in controlling symptoms in many severe cases of generalized urticaria and angioneurotic edema. The marked sedative and hypnotic action obtained from small intravenous doses was also considered a helpful adjunct in the treatment of "status asthmaticus."

Rickettsialpox in New York City*

MORRIS GREENBERG, M.D.

New York, New York

RICKETTSIALPOX is a disease of rickettsial origin first recognized in New York City in 1946 in the course of the investigation of an epidemic of an exanthematous disease. It is characterized clinically by the appearance of an

symptoms and a little later by (3) a papulovesicular rash.

1. *Initial Lesion.* The initial lesion begins as a rounded firm, red papule which grows in size until it attains a diameter varying from 1 to 1½ cm. The center of the papule

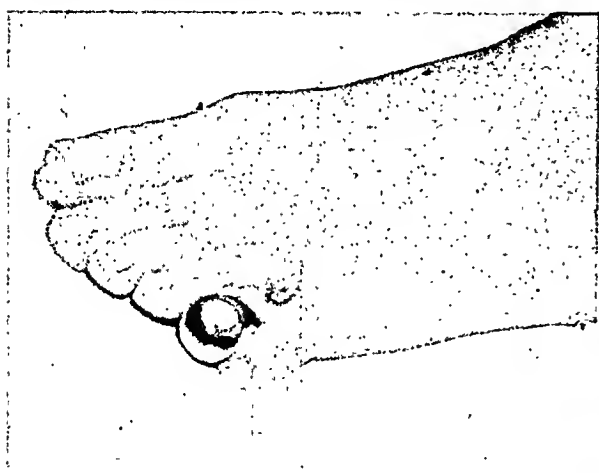


FIG. 1. Initial lesion of rickettsialpox in interdigital space between fourth and fifth toes. (A button has been placed between the toes to bring out the lesion more clearly.) (GREENBERG and PELLITTERI. *Bull. New York Acad. Med.*, June, 1947.)



FIG. 2. Primary lesion on the left arm in crusted stage. (GREENBERG, PELLITTERI, KLEIN and HUEBNER. *J. A. M. A.*, March 29, 1947.)

initial lesion somewhere on the body, followed in about one-half to one week by an acute onset of illness with fever, headache, backache and other symptoms and finally by a generalized papulovesicular rash. The acute illness and rash last about one week each, and the entire course from onset of the initial lesion is about three weeks.

CLINICAL FINDINGS

The disease is characterized clinically¹ by a triad consisting of: (1) an initial lesion followed in about three days to a week by (2) an abrupt onset of fever and other

becomes vesiculated within a few days after onset, the vesicle then shrinks and dries forming a black eschar. (Figs. 1 and 2.) The skin around the papule is at first normal but later becomes erythematous. The lesion is not tender nor does it itch. Patients are frequently unaware of the initial lesion until it is called to their attention later in the disease. After about three weeks the scab falls off leaving a small scar. The regional nodes usually become enlarged but are not tender or only slightly tender to the touch.

* From the Bureau of Preventable Diseases, New York City Department of Health, New York, N. Y.

The initial lesion has been observed on practically all parts of the body; it probably represents the site of entry of infection. It was seen in about 95 per cent of the patients examined by us.

2. *Onset.* The onset of acute symptoms is sudden and occurs about four to seven days after the beginning of the initial lesion. The characteristic symptoms are fever, chills or chilly sensations, sweats, headache, backache, lassitude and photophobia. The fever frequently reaches 103 or 104°f., with morning remissions and usually persists, with the other symptoms, for about a week. Chills or chilly sensations and sweats may recur two or three times a day for the first few days. After about a week the fever defervesces and the other symptoms abate.

3. *Rash.* The rash appears on the same day or even several days after the onset of acute symptoms. (Fig. 3.) The lesions resemble the initial lesion but are usually smaller. They are at first maculopapular but later become vesicular; the vesicles dry and the scabs ultimately fall off without scar formation. The lesions are discrete and generalized except that they are seen only rarely on the palms and soles. They may be abundant, moderate or scanty in number. Lesions have been observed on the tongue and palate. The duration is about a week. After the scab has fallen off a brownish discoloration of the skin may persist for several days. No subjective symptoms accompany the rash.

Except for the triad of symptoms just discussed there are no unusual physical signs. Pulse usually follows the course of the fever, respirations are normal and heart and lungs appear normal on physical examination as well as by x-ray. Occasionally the spleen is enlarged; lymphadenopathy is uncommon. There have been no complications and no deaths.

LABORATORY FINDINGS

The usual laboratory determinations were essentially negative except for moderate leukopenia during the febrile period which returned to normal as a rule about two to



FIG. 3. Rash of rickettsialpox. (GREENBERG, PELLITTERI, KLEIN and HUEBNER. *J. A. M. A.*, March 29, 1947.)

three weeks after onset of the acute illness. Urine examinations occasionally showed transient albuminuria at the height of fever. Sedimentation rates were slightly elevated, red blood counts were normal and blood cultures were sterile. In the patients in whom chemical determinations of the blood were made, normal cholesterol, sugar, non-protein nitrogen and chlorides were found and the icteric index was not elevated. Total serum protein and albumin-globulin ratio were also found to be normal. There was no change in the blood pressure nor in the electrocardiogram. Serologic reactions were negative for brucellosis, tularemia, typhoid, paratyphoid A and B and leptospirosis. The Weil-Felix reaction with *Bacillus proteus* OX19, OX2 and OXK was negative during the convalescent as well as acute stage of the disease, except occasionally in insignificant titers;² the heterophile antibody reaction was likewise negative. The complement fixation reactions of the blood serum were negative for syphilis, psittacosis, murine, epidemic and scrub typhus and Q fever. A few sera were tested by Dr. Herald Cox for

African tick fever and were also found negative.

EPIDEMIOLOGY

The original epidemiologic study was made in the borough of Queens in New York City by the New York City Department of Health in cooperation with the U. S. Public Health Service.³ The epidemic was sharply localized to a group of sixty-nine three-storied houses in three oblong blocks, each block consisting of twenty-three connected houses. They were occupied by 483 families with a total population of about 2,000, of whom 600 were children under fifteen years of age. During the period of study, July to October, 1946, 124 cases were found, an incidence of 6.2 per cent. The rate was 5.3 per cent in children and 6.5 per cent in adults, about equally divided between the sexes. The first cases were reported by physicians practicing in the neighborhood who thought the illness might be atypical chickenpox, a mild form of spotted fever, a form of Brill's disease or some new syndrome. As our studies progressed and the findings were passed on to them the significance of the various features of the clinical picture became manifest.⁴

It was realized early in the study that age, sex and occupation bore no relationship to incidence of disease. It was also obvious that the disease had not been imported since almost all residents had lived in the same apartments for several years and with rare exceptions none of the ill individuals had been away from the city for more than a month preceding onset of illness. Food as a source of infection was also eliminated since no meals were eaten in common by the ill individuals and food supplies were obtained from the same shops by ill and well alike. All milk used was pasteurized and the water supply came from the New York City system. The plumbing was in excellent sanitary condition and there was no evidence of recent breakdown. Examination of water samples indicated no contamination.

Sanitary inspection of the involved houses and the surrounding neighborhood yielded

meager results. The vacant lots were clean, shrubbery and seeded areas were well kept and no garbage or other objectionable matter was found. Two stables and two dog kennels in the vicinity were also found to be clean and well kept. Dogs belonging to residents of the development as well as those in the kennels were free of ticks as was the shrubbery in the housing development and in the vacant lots. The only insects seen were common house flies and dog fleas. In spite of a heavy precipitation only one mosquito breeding impoundment was found in the basement of an unfinished house near the development. Larvae were found in this water and the adults were collected from the ceiling of the basement; they were identified as *Culex pipiens* by Dr. Alan Stone of the U. S. National Museum. Adults of the same species were also found in the basements of the houses under investigation and tests showed them to be non-infectious.

Preliminary epidemiologic investigations pointed to the houses themselves as the site of the source of infection. The only factor common to all the patients was the presence of field or house mice in the houses and surrounding courtyards. All the tenants were aware of their presence. They were seen in the basements, in apartments, in the courtyards and were heard scampering up and down the walls. Dead mice were found in courtyards, basements and apartments. Mouse droppings were found everywhere, including the floors, tables and beds. The possibility that the mice played a part in transmission of the disease suggested itself and a decision was reached to trap them and comb them for parasites. A field laboratory was set up in one of the buildings and traps were set out in many places. In the meantime mites were found in mouse harborages and on incinerator walls (in the basements) by Mr. Charles Pomeranz. After the mice were trapped and combed similar mites were recovered as ectoparasites. They were identified as *Allodermanyssus sanguineus* (Hirst) by E. W. Baker of the Bureau of Entomology and

Plant Quarantine of the U. S. Department of Agriculture.

A systematic collection of mites from walls, mouse nests and trapped mice was begun in the buildings by means of a suction apparatus. Entry was not obtained in nine of the houses but a search was made in the remaining sixty. An attempt was made to correlate the cases of illness with the presence of mites in the houses of residence. In forty-one houses no mites were found and in these houses there were forty-two cases of illness, an incidence of one patient per house. On the other hand mites were found in nineteen of the houses and sixty-seven cases were reported in these houses, an incidence of 3.5 patients per house. Furthermore, there appeared to be a rough correlation between the number of cases reported from a house and the quantity of mites found there. In each of two houses in which mites were found in large numbers eight cases of illness as compared with an average of 3.5 cases were observed. Multiple cases in a family were not unusual, four cases occurring in each of four families, three cases each in seven, and two cases each in twenty families. None of the sick individuals recalled being bitten by mites or observing them on their bodies, but that is not surprising in view of the smallness of the mite, its absence of color before engorgement and its ready destruction by the rubbing of a finger. One should keep in mind that individuals rarely remember the bite of a tick, an arthropod many times larger than a mite. That the mites found in the buildings were blood sucking was readily observed when they engorged after attaching to mice; furthermore, smears made from those that were found engorged showed mammalian erythrocytes. Although mites were not observed in the apartments by the residents, several housewives in whose families cases were reported had observed tiny blood spots on the bed sheets.

Epidemiologically, a case could be made out against the mites which were apparently infected. How they were introduced into the buildings was a matter of conjecture. How-

ever, once introduced they survived and propagated by obtaining blood meals from the mouse which served as a reservoir. When introduced accidentally into the apartments, they readily infected humans by a bite or possibly by the rubbing in of their feces, causing a primary lesion at the site. Propagation of the virus in the human host caused the acute symptoms and rash. To prove this hypothesis it was necessary to recover the infecting virus from the vector, the reservoir and the human host.

PATHOLOGY

Since all patients have survived, examination of pathologic material is limited to biopsies of skin lesions and of a regional lymph node.⁵ The skin lesions showed aggregations of small and large mononuclear cells around the blood vessels, especially near sebaceous glands. The capillaries showed swelling of the endothelium which bulged into the lumen almost obstructing it. Strands of fibrin were seen in the lumen of some superficial capillaries. Mast cells were observed among the cells forming the perivascular collections, around hair shafts, some sweat glands and occasionally in the derma. In the lymph node there was marked hyperplasia of the reticulum cells in the cortex. The small blood vessels appeared narrowed; they were lined with tall, cuboidal epithelial cells. Numerous mast cells and few eosinophiles were seen. In none of the sections were rickettsial-like bodies observed. However, the pathologic picture resembled that seen in typhus fever and Rocky Mountain spotted fever.

ETIOLOGY

While the epidemiologic studies were in progress, blood specimens were obtained from a number of the patients in the acute stage of the disease and injected intraperitoneally into mice and guinea pigs.⁶ Illness in the mice was characterized nine days later by inactivity, rapid breathing and ruffled fur. Pathologically, the mice showed enlarged lymph nodes, a large

edematous liver and a tremendously enlarged and engorged spleen. Suspensions of liver and spleen were passed serially in mice and always produced the same symptoms and pathologic conditions. In guinea pigs the suspension caused scrotal swellings and fever in three to four days. Suspensions of brain from the original mouse were injected into other mice and caused symptoms but no deaths. Brain removed from one of the sick mice on the twelfth day after inoculation was inoculated in a saline suspension into the yolk sacs of embryonated eggs. In a week the embryos were moribund or dead. Films made from the yolk sacs showed numerous intracellular and extracellular diplobacilli which stained well by Machiavello's method but poorly with methylene blue. Yolk sac suspension grew well when passed in other eggs and caused illness in mice and guinea pigs similar to that caused by the animal passage material. It was not possible to cultivate it on acellular media.

The recovered organism was tested by the complement fixation reaction against serums from normal humans as well as of recovered patients, and from patients with Rocky Mountain spotted fever, endemic typhus, tsutsugamushi and Q fevers and syphilis. There was a high degree of specificity except for cross reactions with Rocky Mountain spotted fever. Serums from recovered patients gave positive results in high titers. When blood was obtained early and later in the disease, significant rises in titer were demonstrated. The same serums tested against Rocky Mountain spotted fever antigen gave positive results in about 80 per cent of the cases, usually in a lower titer, but when tested against the antigens of psittacosis, epidemic and endemic typhus, tsutsugamushi and Q and Colorado tick fevers the results were negative.

The Weil-Felix tests with *Proteus* OX19, OX2 and OXK performed with the serums of recovered patients were negative or occasionally positive in insignificant titers. The name rickettsialpox was given to the disease since it is characterized clinically

by the appearance of pocks and is caused by a rickettsia.

Organisms identical with those obtained from human patients were recovered from six pools of mites collected in the buildings under investigation.⁷ The mites were ground up and injected intraperitoneally into adult male guinea pigs. Fever and scrotal swelling were observed on the fourth day. Tunica washings caused similar illness in other guinea pigs and characteristic illness in mice. In chick embryos they caused death on the seventh day after yolk sac inoculation and smears from the yolk sac stained by Machiavello's method showed intra- and extracellular red diplobacilli similar to rickettsiae. When these organisms were used as antigen in the complement fixation test with normal human serum and with convalescent guinea pig serum of endemic typhus, Q fever, Rocky Mountain spotted fever and rickettsialpox, positive reactions were obtained with the last two only, a result similar to that obtained with rickettsialpox antigen. Furthermore, guinea pigs convalescent from rickettsialpox were immune to the mite strain.

Flat mites obtained from some of the buildings were allowed to engorge on a laboratory mouse. Ten days later the mouse became ill. Its brain was removed and a saline suspension injected into embryonated eggs. In seven days the embryos died and smears from the yolk sacs showed numerous rickettsiae. Antigens from these yolk sacs gave complement fixation reactions similar to those obtained with the human and with the other mite strains. The name *Rickettsia akari* was given to the agent recovered from humans and mites.

The recovery of *R. akari* from mice trapped in the buildings was accomplished last.⁸ Saline suspensions of liver and spleen from the trapped mice were injected intraperitoneally into groups of laboratory mice. Nine days later they showed characteristic illness. Passage to mice and guinea pigs was accomplished with suspensions of tissue of the sacrificed mice. *R. akari* was recovered from the tissues of both the mice and guinea

pigs, and growth in egg yolk sac was obtained with tunica washings of the latter. Cross immunity was demonstrated among the human, mite and mouse strains.

DIFFERENTIAL DIAGNOSIS

Rickettsialpox bears a certain resemblance to several other diseases from which it should be differentiated:

Chickenpox. This is the disease with which it has been most frequently confused because of the occurrence of vesicular lesions in both diseases. However, in chickenpox the entire papule becomes a vesicle so that in a certain stage of the disease only vesicles are seen on the body. They are thin walled and easily broken. In Rickettsialpox the papular element of the lesions remains throughout, the vesicles surmounting the papules. No initial lesion is seen in chickenpox and the fever does not precede the rash. Also, adults are uncommonly affected which is not true of rickettsialpox. Finally, the complement fixation reaction is specific for the latter.

Smallpox. This is a more serious disease. Headache and backache precede the onset of fever, symptoms are more severe, the rash becomes pustular and lasts much longer than in rickettsialpox, there is no initial lesion and mortality is high.

Infectious Mononucleosis. A rash is only an occasional feature in this disease. The blood picture is characteristic and the heterophile reaction is usually positive. Finally, the specific complement fixation reaction in rickettsialpox should distinguish the two diseases.

Other Rickettsial Diseases. (1) *Rocky Mountain spotted fever:* There is usually a history of a tick bite, the rash is macular, papular or petechial, not vesicular, there is no initial lesion and the symptoms are more severe with a fairly high mortality rate. Furthermore, leukopenia is not characteristic and the Weil-Felix reaction is usually positive with Proteus OX19 and OX2.

(2) *Epidemic typhus:* There is usually a history of infestation with lice. Patients are sicker and frequently die. There is no

initial lesion and the rash is not vesicular. The Weil-Felix reaction with Proteus OX19 is positive and the complement fixation reaction is specific.

(3) *Endemic typhus:* This disease resembles rickettsialpox in its comparative mildness. However, the rash is macular or papular and occasionally petechial but not vesicular and no primary lesion is noted. The Weil-Felix reaction with Proteus OX19 is regularly positive and the complement fixation reaction is specific.

(4) *Tsutsugamushi fever or scrub typhus:* There is an initial lesion in this disease as in rickettsialpox. The rash, however, resembles that of typhus fever rather than rickettsialpox, the symptoms are more severe and mortality is high. The Weil-Felix reaction is positive with Proteus OXK and the complement fixation reaction is specific.

(5) *Boutonneuse fever:* There is a considerable resemblance between this disease and rickettsialpox. Both are mild diseases with no mortality and in both there is an initial lesion. However, in boutonneuse fever the rash is not vesicular and it is frequently seen on the soles and palms. History of a tick bite and association with dogs is common and the behavior of the organism in laboratory animals is different in the two diseases.⁶ Finally, the Weil-Felix reaction with OX19 and OXK is usually positive during convalescence from boutonneuse fever.

INCUBATION PERIOD

Incubation period of the disease, the period between the bite by the acarid and occurrence of the initial lesion, was difficult to determine because none of the patients recalled being bitten and almost all had lived in the same house for a long period of time. In one case, however, a woman visited her sick daughter for one day only and then returned home. She observed an initial lesion a week after the visit. One of the investigators came from Montana to the epidemic area and developed an initial lesion fifteen days later; his incubation

period was, therefore, not more than about two weeks. Another patient had been away on vacation and developed a primary lesion fifteen days after her return; here, too, the incubation period could not have been more than two weeks. One individual living in the epidemic area went out of town and developed an initial lesion six days after departure; the incubation period could, therefore, not have been less than six days. From the meager data one can say that the incubation period appears to be between one and two weeks.

TREATMENT

Rickettsialpox is a self-limited disease and the acute symptoms usually do not last more than a week. No complications or deaths have been reported. Specific therapy, such as para-aminobenzoic acid, has not been tried since the symptoms yield readily to ordinary antipyretic and sedative measures.

ENDEMIC FOCI IN NEW YORK CITY

Reports of suspected cases in New York City occurring in locations removed from the epidemic area soon were reported and investigation was made of all of them.⁹ During the second half of 1946, 178 cases, and in the first eight months of 1947, 79 cases were seen in four boroughs of the city. No cases have been reported from Staten Island nor has any authenticated case been reported outside of the city. It is interesting that in the borough of Queens, aside from the epidemic area, only five cases have been seen at a considerable distance from and apparently unrelated to the epidemic. In Brooklyn, the largest borough in the city, only seven unrelated cases have been reported. Most of the cases have occurred on the island of Manhattan and in the adjacent borough of the Bronx, seventy-three in the former and thirty-three in the latter.

Inspection of the spot map of the city indicates that although the cases are widespread they tend to group. Thus in Manhattan no cases have been reported so far

in the lower tip of the island. There is also a free area just above and to the east of Central Park. On the other hand, there is considerable grouping in the lower east side and the lower west side, a less concentrated grouping east and west of Central Park and scattered groups on the west side above the park. In the Bronx five cases are spotted in one house in the upper west region, and several groups are seen in the lower middle and west part of the borough. One case has been reported from a small island just off the Bronx. In Brooklyn there is no close grouping but almost all the cases have been reported from the northwestern part of the borough; in Queens, aside from the epidemic area, only five cases have been reported, four in the northwestern part of the borough not too far removed from the Brooklyn cases and one from the opposite part of the borough.

Multiple cases in the same house occurred regularly in the epidemic area in Queens. Multiple cases in the same house have also been reported in Manhattan and the Bronx. In the latter borough five patients were seen in each of two houses; in one of these houses seven more patients were observed by a physician in the building but were not seen by us. In two other houses two patients were seen in each and a probable third patient in one of them. In Manhattan, too, two patients were seen in each of several houses.

With numerous foci spread all over the city, it appears improbable that the disease appeared *de novo* in 1946 in Queens. It is more probable that the disease existed for some time in an unrecognized form and that it was introduced accidentally into the Queens housing area. The conditions being ripe there an epidemic occurred which because of its extent forced itself to the attention of the medical profession. Had only a few cases occurred they would have been diagnosed as chickenpox or some other entity and the disease would have continued to be unrecognized until some other fortuitous occurrence focused attention upon it.

CONTROL MEASURES

Control measures differ little from those used in the control of rodents causing other diseases, such as murine typhus. A preliminary survey is needed to determine the extent of infection in mice. This can probably be accomplished by the systematic trapping of mice and the testing of their blood for the presence of complement fixing antibodies against rickettsialpox. Such tests were positive in mice trapped in the epidemic area in Queens and in houses where cases had occurred in Manhattan and the Bronx. They were negative in laboratory mice and in those trapped outside of New York City.⁸ After the endemic foci have been mapped out antirodent measures can be carried out, such as baiting, trapping and poisoning and the elimination of rodent harborages. The use of DDT in the destruction of *Allodermanyssus sanguineus* has not yet been tried.

VECTOR

Allodermanyssus sanguineus (Hirst) is a small, colorless mite whose body measures about 1½ mm. in length in the female and about one-half that in the male. When engorged, it swells to many times its size and becomes bright red in color. Although first described in a publication in the United States in 1913 by Stanley Hirst,¹⁰ specimens were received by the Division of Insect Identification of the U. S. Department of Agriculture from the District of Columbia in 1909. Another occurrence of the mite in the United States was recorded by the division between 1909 and 1938. From 1938 to 1946 a number of samples were identified. They came from Tucson, Ariz., the District of Columbia, New York City, Philadelphia, Indianapolis and Boston. Most specimens were found in houses or apartments but some were found on humans.⁷ Hirst's original description of the mites was from specimens recovered in Egypt.¹⁰ Previous to 1946 there is no record of this mite as a vector of disease.

RESERVOIR

The small house or field mouse is the only animal that has so far been implicated as the reservoir. Mice were found in abundance in all the houses in which cases of rickettsialpox were investigated, and mites were found as ectoparasites of the mice in the epidemic area in which trapping and combing were carried out systematically. Hirst's description of the mite is from specimens found as ectoparasites on *Mus rattus*, *Arvicanthis niloticus* and *Acomys cahirinus* in Assiut, El Hasaiba, Deirut and Kaus in Egypt.

SUMMARY

Evidence has been presented of the occurrence of a newly recognized disease, rickettsialpox, in New York City which occurred in epidemic form in a localized community in the summer of 1946 and has been occurring endemically since. Clinically, it is characterized by the appearance of a painless initial lesion on some part of the body, followed in about a week by an acute onset with fever, headache, backache and other symptoms and by a generalized papulovesicular rash. Routine laboratory examinations are negative except for leukopenia. The disease is caused by *R. akari* and is transmitted by a mite, *Allodermanyssus sanguineus* (Hirst), the reservoir for which is the house or field mouse. The organism has been recovered from the blood of patients, from the mites and from infected mice. Serums of recovered patients give a negative Weil-Felix reaction but a positive complement fixation reaction for rickettsialpox. The disease is self-limited and the treatment is symptomatic. No deaths have been reported.

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Seminars on Hypertension

Consideration of Human Hypertension with Respect to Its Renal Origin and Therapy*

WILLIAM GOLDRING, M.D.

New York, New York

THE Seminars on Hypertension which have appeared in the *American Journal of Medicine* have emphasized the numerous technics and varied points of view concerned with this problem. Some of the papers have been purely descriptive, others have speculated on the pathogenesis of experimental renal hypertension and human essential hypertension and some have presented data on various types of medical and surgical treatment for human hypertension. It would be expected from the tentative nature of present information concerning hypertensive disease that a number of controversial issues would be raised. These issues have been fairly presented by the various authors with a statement of their personal preferences in each instance.

It is the purpose of this paper to restate some of the controversial issues for further appraisal. It is obvious, of course, that such reappraisal is no more than a statement of agreement or disagreement of another group of observers who make no claim to finality in any of their opinions.

In deciding on the papers to be selected for this summary the purely descriptive studies were omitted since nothing could be accomplished but recapitulation, and the studies dealing with the pathogenesis of hypertension were omitted because of the lack of sufficiently definitive data on which to take even a tentative stand at this time. There remain for the purposes of this discussion those studies dealing with the

similarity between experimental renal and human hypertension and those dealing with the treatment of human hypertension.

SIMILARITY BETWEEN EXPERIMENTAL RENAL HYPERTENSION AND HUMAN HYPERTENSION

The demonstration by Goldblatt and his associates that partial constriction of the renal arteries of an animal leads to persistent diastolic and systolic hypertension opened a new field for investigation of human hypertension.¹ One problem in man appeared to be partly clarified, i.e., the probability that the mechanism of hypertension in primary bilateral intrinsic renal disease might arise from the kidneys, even though this assumption still leaves the exact pathogenesis of elevated blood pressure in doubt. The observation of Goldblatt and associates has contributed little to understanding of the etiology of human essential hypertension and it is not yet established that fundamental disturbances in the experimental animal and in the human are identical in nature.

As pointed out by Dexter,² in spite of numerous studies, there is as yet no unequivocal explanation of the mechanism of experimental renal hypertension, and no more than a small beginning has been made in uncovering the pathogenesis of human essential hypertension.

In the first paper of these seminars Goldblatt³ presented evidence for and against the similarity of mechanism in experimental renal hypertension and human essential

* From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

hypertension; the net of his evidence spoke for a striking similarity. On the other hand, Goldring, Chasis and Smith⁴ found the evidence for similarity in mechanism was unconvincing. They stated, "If it is predicated that alteration in renal hemodynamics is the primary disturbance underlying essential hypertension, the factors giving rise to this alteration must be sought in anatomical faults affecting some greater or lesser fraction of the renal circulation. Such anatomical faults are not, as a rule, distributed symmetrically, and would not, except in rare instances, alter renal hemodynamics symmetrically." Nevertheless, among twenty-one unselected hypertensive patients studied by us, alteration of renal hemodynamics was identical in the two kidneys; not a single patient showed unilateral renal impairment.⁵ This circumstance is compatible only with the view that the underlying cause of the disturbance in renal circulation operates equally in both kidneys. It is difficult to see how this could be the case if alteration in renal hemodynamics *per se* is the primary factor.

Diminished renal blood flow is a common accompaniment of essential hypertension in man. Present evidence, however, indicates that this renal circulatory alteration is not the primary and presumably the initiating factor, but rather a secondary effect resulting from the action of a humoral pressor agent of unknown origin.⁶

It can be accepted that experimental renal hypertension has its counterpart in some forms of unilateral and intrinsic bilateral renal disease in man, but this renal type of hypertension appears to be relatively infrequent, accounting for probably no more than 10 per cent of the incidence of hypertension in adults. The occurrence of some instances of renal hypertension must not lead us into accepting renal origin as the universal rule.

The incidence of hypertension in patients with urologic disease is no greater than in the general population without urologic disease. Friedman, Moschkowitz and Marcus⁷ found an incidence of hypertension of

21.8 per cent in 193 patients with unilateral renal disease proven at operation while in a control group of 1,006 living patients the incidence of hypertension was 22.8 per cent. Oppenheimer, Klempner and Moschkowitz⁸ found a 27.5 per cent incidence of hypertension in seventy-nine necropsied patients with unilateral renal disease while in 333 control necropsies the incidence of hypertension was 24 per cent. Baggenstoss and Barker⁹ similarly found an identical incidence of hypertension in patients with and without unilateral renal disease (29.3 per cent and 29.0 per cent, respectively) while Braasch, Walters and Hammer¹⁰ found an 18.7 per cent incidence of hypertension in 1,684 living patients requiring renal surgery, a figure essentially identical with the incidence of hypertension in 175 living controls (20 per cent). Last, Crabtree and Chaset¹¹ found only a 9 per cent incidence of hypertension in 150 patients who had been subjected to nephrectomy for unilateral renal disease.

If it is assumed, as some do, that renal vascular disease, structural or functional, is the primary cause of the development of human essential hypertension and, in the causal sense, precedes all other manifestations of the disease, then admission that vascular disease precedes hypertension leaves the mechanism of the vascular disease unexplained and the etiology of hypertensive disease still unknown. Moreover, sclerosis of the renal arterioles is not invariable early in the course of hypertensive disease. Indeed, admitting the validity of their conclusion, Castleman and Smithwick¹² report that it is absent or minimal in about one-half the patients on whom they had biopsy studies. It seems hazardous to us to base conclusions regarding etiology, pathogenesis or therapy in man on the assumption that the single hemodynamic alteration of elevated blood pressure in the experimental animal is analogous to the disease as it occurs in man.

Human hypertensive disease is a complex disorder of which elevated blood pressure is merely one manifestation. Production of

elevated blood pressure in the experimental animal cannot be construed as evidence of the production of hypertensive disease, nor can the assumption be accepted that when blood pressure is elevated the animal has developed the counterpart of the human disease, nor that when blood pressure is lowered to normal levels by presumably specific antipressor agents the animal is cured of the disease. The hypotensive action of such substances as renal extract in experimental renal hypertension cannot be accepted as evidence of specific cure since several investigators admit that the actual causative agent or agents of experimental renal hypertension is still unknown.

The general picture is such that we see no reason for modifying our position as summarized by one of us (H. W. S.)¹³ "To read the rapidly expanding literature on this subject is only to discover the complexity of the problem of ultimate etiology. One observer holds that hypertension is of dietary origin, while another relates it to climate, both interpretations being far from negligible, since the incidence of the disease is remarkably low among many primitive peoples. By other observers, it is contended that there is a distinct hereditary trend, at least in predisposition, while correlations with endocrine imbalance are not lacking. At the other extreme, the psychoanalyst tells us that the early fluctuating phase of essential hypertension is a manifestation of a psychoneurosis based on excessive and inhibited hostile impulses; and again, that inhibition of heterosexuality or repression by a dominant parent, with chronic, hostile, but unsuccessful, rebellion against submissiveness, are common psychological features of the disease.

"In the present state of our knowledge, it would be hazardous to advance the kidneys as more than one contributor to a malignant mélange, which, if we are to accept a fraction of the evidence, is a constitutional disorder involving in addition to the kidneys, the vascular bed, the vasomotor centers, the cerebral cortex, perhaps the entire organism and its genetic foundations. And yet,

considering the tentative nature of most of the suggestions which have been made in regard to etiology, it is unnecessary to magnify them.

"When and if it can be demonstrated that the relief of altered renal hemodynamics specifically abolishes all signs of hypertensive disease in man, then the major link in the chain of logic which incriminates the kidneys will be complete. This is asking that we reach our desideratio summa, the cure or prevention of the disease, at the beginning of our problem, which is perhaps more than we can expect, but short of this demonstration, it is impossible to charge the kidneys with the sole responsibility in human hypertensive disease."

TREATMENT

In no other disease have so many therapeutic procedures been conceived, tried and discarded. This circumstance is understandable in view of its great prevalence and potentialities for ultimate harm, a circumstance which instills desperation in both patient and doctor. The history of therapy in hypertensive disease is replete with instances of unwarranted enthusiasms and baseless claims. Unfortunately the period of unwarranted enthusiasms and baseless claims has not passed and is not likely to pass until discovery of the ultimate cause or causes.

Perhaps the most important single obstacle to a clear interpretation of the effect of a therapeutic procedure is the complete reliance on the level of the blood pressure, a measurement so crude and variable as to be almost wholly without value as a guide to therapeutic effectiveness. The best that can be said for the blood pressure level is that it is a consistent sign of hypertensive disease and that its measurement is easily available. It seems clear that the measurement of a more fundamental and less variable manifestation of the disease is urgently needed for evaluation of therapeutic effect. This limitation introduces a considerable hazard in the assessment of any type of therapy for hypertension. It is a

further fact that morbidity and mortality in hypertensive disease are directly due to vascular disease. Treatment which lowers blood pressure, therefore, is beneficial only in the view that vascular disease is a consequence of the blood pressure level. However, the relationship between hypertension and vascular disease is not fully understood. Until this relationship is clarified the rationale for therapeutic measures in hypertension designed solely to lower blood pressure cannot be accepted without question.

Richard Bright established the first fact, i.e., that obstruction of blood flow through the kidneys precedes and accounts for hypertension, which in the absence of blood pressure measurement at that time was expressed as cardiac hypertrophy. Further observation by other investigators uncovered instances of prolonged hypertension in which at necropsy the vascular involvement of the kidneys was clearly insufficient to result in significant obstruction to blood flow. From this observation arose the second thesis, i.e., hypertension was due to functional vasoconstriction and renal and splanchnic vascular disease is a consequence of the elevated blood pressure. More recently a third point of view has been introduced suggesting that elevation of blood pressure and vascular disease are concomitant effects of an unknown mechanism and independent of each other. The evidence to support each of these three contentions is circumstantial and as yet it is not possible to have full confidence in any.* Consequently, present day treatments using lowering of blood pressure as the guide must be considered empirical.

LOW SALT DIET IN THE TREATMENT OF HYPERTENSION

A diet containing less than 200 mg. of sodium has been suggested for the treatment of human essential hypertension. In the past few years it has been applied extensively.

* The single exception in this controversy applies to primary bilateral renal diseases as glomerulonephritis, pyelonephritis and polycystic renal disease in which it is generally believed that renal disease precedes and accounts for hypertension.

The rationale of the sodium restricted diet is far from clear. However, its proponents adhere to the thesis that the adrenal cortex is involved in the genesis of essential hypertension. They point to two principal lines of evidence suggesting disturbance of sodium metabolism: one is that the blood sodium to chloride ratio is higher in hypertensives than in normotensives and the other is that on a rigid twenty-four-hour sodium chloride restriction, normotensive subjects lose weight and develop diuresis whereas hypertensive patients do not. Other investigators have been unable to confirm these observations.

Even admitting the possibility of participation of the adrenal in the genesis of hypertension, it seems clear that modification of a secondary effect, namely, abnormal sodium retention could not be expected to correct a primary underlying adrenal cortical disturbance. Sodium restriction, therefore, resolves itself into another treatment designed to lower blood pressure without regard to its underlying cause and, therefore, is a treatment of doubtful value.

While some of the earlier studies have indicated an occasional significant effect of this diet on the blood pressure level, more recent reports have been decidedly disappointing. The more one takes into account the great variability of the blood pressure level and the more insistence is placed on a prolonged and adequate control period, the more obvious it appears that a sodium restricted diet does not significantly lower blood pressure.

In connection with the practical application of the sodium restricted diet and even allowing for apparent moderate diminution of blood pressure in some patients, Perera¹⁴ makes the following statement: "There is nothing to suggest that the small changes in resting blood pressure associated with rigid sodium chloride withdrawal are of therapeutic significance or that prolonged restriction will exert any influence on the natural history of this disorder (hypertensive disease)." This reviewer is in full accord with the attitude as expressed and

finds it most refreshing at a time when the literature is filled with enthusiastic overstatements concerning treatment of a disease about which so little is known.

RICE DIET IN THE TREATMENT OF HYPERTENSION

Among the numerous theories advanced to explain the pathogenesis of hypertension, one is concerned with failure of deamination. The final breakdown of amino acids is brought about by two separate processes: decarboxylation which can occur in the absence of oxygen and deamination which requires the presence of oxygen. Failure of deamination, therefore, would permit amines to enter the systemic circulation and since many amines are known to be pressor in their action hypertension could result. It is clear from these facts that failure of deamination could occur as a result of a deficiency of aminase, the action of an inadequate aminase or as a result of the action of normal aminase in the absence of adequate available oxygen. Since there is no known means to improve or increase amine oxidase activity and no means to make more oxygen available in the kidneys, the alternative is to decrease quantitatively the amount of amino acid which reaches the kidneys and other tissues in which deamination is known to occur. It should be stated at this point that beyond inference, disturbances of renal metabolism have not as yet been shown to be involved in the pathogenesis of human hypertension.

The rationale of the rice diet in the treatment of hypertensive disease is an extension of this general thesis. In an early report Kempner¹⁵ proposed the following as a working hypothesis: "If for the moment we disregard the renal excretory function and consider the kidney only as an organ of metabolism, we can assume, as a basis for experimental approach, that pathological conditions in the kidney may lead to the following changes:

"a) Substances which are normally removed by the kidney cell metabolism may

increase in amount in the blood or tissue fluids.

"b) Substances which are normally produced by the kidney cell metabolism may decrease in amount.

"c) Some of the substances normally metabolized by the kidney cells may be metabolized vicariously by the liver cells, with a resulting increase in the metabolic products of the liver cells.

"d) 'Abnormal' substances may appear in blood or tissue fluids which under physiological conditions exist only in an intermediary, non-apparent phase of the kidney cell metabolism since normally they are immediately further metabolized to harmless end products.

"If we assume that some of these 'abnormal' substances which appear when the metabolic function of the kidney cells is disturbed are harmful and play a role either directly or indirectly in the development of hypertension, vascular retinopathy, encephalopathy, heart lesions and new kidney disease, the working hypothesis suggests itself; that the ordinary mixed diet may contain constituents which increase the production of these 'abnormal' harmful substances by the diseased kidney cells."

Kempner¹⁶ further states that the experimental basis for application of the rice diet in treatment of human hypertension rests on "observations made on the protein, fat and carbohydrate metabolism of isolated kidney cells under various pathological conditions (cell injury and/or changes in pH, sodium bicarbonate concentration, oxygen tension and metabolizable substrate)."

The rice diet contains 300 Gm. of rice. The protein content of the diet is 20 Gm.; fat 5 Gm.; sodium 150 mg.; chloride 200 mg. and carbohydrate in sufficient amount to bring the total caloric value of the diet to 2,000; supplementary vitamins are added. The carbohydrates are taken in the form of fruit juices and sugar. Fluid intake is limited to 1 L. a day. Balance studies on patients taking the rice diet indicate that they are in nitrogen balance in spite of the apparently low protein intake. As a rule,

there is an initial weight loss of about 10 pounds during the first week of this diet after which the patient maintains his weight. This diet has been tried extensively on hypertensive patients since its introduction in 1944. It has aroused a great deal of interest and discussion, reminiscent of the initial attitude toward all forms of therapy which have so far been introduced in the treatment of hypertension in man.

Opinions in regard to the effectiveness of the rice diet have varied from brilliant to insignificant. There have been a few equivocal reports, but most of these investigators have attributed the moderate falls in blood pressure which they observed to the low sodium content rather than to the low protein content or any other specific character of the rice diet. The use of low sodium intake in the treatment of hypertension has been discussed under another heading.

In reviewing the various studies it is a striking fact that the most favorable study of all was conducted without regard to the establishment of adequate pretreatment control levels for blood pressure whereas in the unfavorable studies such a control was rigidly applied before institution of the rice diet. Even the most casual contact with hypertensive patients over a period of time makes it clear that when such a rigid control of the blood pressure level is lacking it is quite impossible to assess intelligently any fall in blood pressure on any form of therapy. It is quite apparent to those who see the need for a control period prior to treatment that it often takes two weeks and occasionally as long as six weeks in a hospital environment before the blood pressure becomes sufficiently stabilized to permit introduction of a new variable in the form of treatment. If one includes only those studies in which this control period has been properly carried out, it can be stated without equivocation that the rice diet has no effect on the level of the blood pressure.

However, proponents of the rice diet in the treatment of hypertension point to the

astounding incidence of reversal of the so-called "hypertension pattern" of the electrocardiogram toward normal, diminution of the size of the heart and regression of papilledema. It is these objective evidences of the effect of the rice diet which are urgently in need of explanation. Regression of these objective evidences of hypertensive disease even when the blood pressure level has not been lowered either suggests correctness of the hypothesis that elevated blood pressure is a concomitant disorder and unrelated to the presence or progression of vascular disease, or that we do not as yet fully appreciate the enormous potentiality for spontaneous variation in the untreated hypertensive patient.

However, these striking data come from the one source which has reported brilliant results with the rice diet treatment¹⁵ and as yet there has been no confirmation from other observers. Until such confirmation is available, the rice diet does not warrant any more than casual interest.

SURGICAL TREATMENT OF HYPERTENSION

Unilateral Nephrectomy. It has been amply demonstrated in the experimental animal that partial constriction of the main renal arteries to both kidneys invariably results in persistent elevation of systolic and diastolic blood pressures. However, observations on the blood pressure-raising effect of unilateral renal artery clamping are meager. Such data as are available indicate that persistent blood pressure elevation commonly follows unilateral constriction in the rat, but the frequency of spontaneous bilateral renal disease in this experimental animal leaves considerable doubt as to the validity of this observation. The few observations that are available on the effect of unilateral renal artery constriction in the dog indicate that increase of the blood pressure is quite uncommon and only transient. While there are reported instances of persistent elevation of blood pressure in the dog after unilateral renal artery constriction, they are exceptional; even more

exceptional is the demonstration that such blood pressure returns to normal upon removal of the operated kidney some months after constriction. In view of the rarity of persistent hypertension following unilateral renal artery constriction in the dog and the infrequency of cure in these following nephrectomy, acceptance of unilateral renal artery constriction as a mechanism in the pathogenesis of even experimental renal hypertension would appear to be hazardous and certainly offers little or no basis for transferring this mechanism and cure to human essential hypertension. Yet these meager and inconclusive observations supply the rationale for nephrectomy in hypertensive man.

It would be supposed that if unilateral renal disease can initiate hypertension in man, the incidence of hypertension would be greater in patients with unilateral renal disease than in a control group of normal subjects. However, available statistical evidence clearly indicates that the incidence of hypertension is similar in both groups. In 585 published instances of various unilateral renal diseases the incidence of hypertension was 24.2 per cent; in 433 necropsy controls the incidence of hypertension was 26.5 per cent and in 2,928 living controls the incidence of hypertension was 26 per cent.¹⁷

In his recent and detailed analysis of all available data bearing on the incidence of hypertension in unilateral and bilateral urologic diseases, Smith¹⁸ stated, "to conclude on the basis of the above data that perhaps as many as 10 per cent of hypertensives have demonstrable urologic abnormalities of such a nature as to lead to functional impairment (and the figure 10 per cent seems generous in view of the data of Ratliff, Beehgaard, Pearman, Braasch and their co-workers), is no warrant for inferring that in these 10 per cent the urologic disease is responsible for the hypertension. The probability of coincidence is very great. At the present time the only way a causal relationship can be demonstrated in any particular case is by

curing the hypertension by removing the offending organ." However, despite the lack of an acceptable experimental basis and failure of convincing statistical support from observations in man apparent cures have been reported. Even when strict criteria are demanded, Smith¹⁸ has pointed to 47 cases of 242 reported operations which must be accepted as instances of apparent cure. His requirements for "successful" unilateral nephrectomy included the establishment of persistent preoperative hypertension with adequate control of the blood pressure level, fall of the blood pressure into the normal range promptly after the operation and persistence in the normal range for one year or more.

While these patients must be considered probable cures, the variable and often unpredictable course of the blood pressure level is of such magnitude that acceptance of this therapeutic procedure must for the present remain tentative. In spite of these rare but apparently successful instances, enthusiasm for unilateral nephrectomy in the treatment of hypertension is distinctly on the wane, and even its strongest proponents are emphatic in stating that decision to remove a kidney should rest altogether on the urologic indications and not upon the hope of removing the cause of hypertension; before nephrectomy is performed the diseased kidney should be shown to be practically devoid of function and the opposite kidney free of disease.

Sympathectomy. The rationale of sympathectomy rests on the concept that so-called essential hypertension begins as a functional vasoconstrictive disease mediated through the sympathetic nervous system. In this view hypertension is the initial clinical evidence of the disease and arteriolar sclerosis is a direct result of the elevated pressure. Surgical interruption of these pathways, therefore, would in theory prevent vasoconstriction, hypertension and arteriolar sclerosis. It would appear, then, that the rationale for sympathectomy rests upon arbitrary selection of one of the three current hypotheses previously mentioned

concerning the interrelationship between hypertension and vascular disease.

After observations on about 6,000 sympathectomized patients by numerous observers opinions vary from insignificant to brilliant results. The ideal patient for sympathectomy has been characterized as the early labile hypertensive by some and the late hypertensive with advanced vascular disease by others of equal experience with this form of treatment. After many attempts it is generally agreed that no satisfactory preoperative guide exists which might be helpful in anticipating the effect of sympathectomy. The wide differences of opinion in regard to the value of this treatment rest upon the unpredictable natural history of the disease in any single individual. Conclusive opinion is further made difficult by dependence on a comparison of blood pressure levels before and after operation, a measurement more unpredictable and undependable as a basis for opinion than any other single evidence of the disease. In short, the extremely variable course of hypertensive disease makes it impossible to obtain a satisfactory control.

However, in spite of these practical objections to easy acceptance of sympathectomy as a useful therapeutic measure it must be admitted that there are occasional instances of what appear to be striking arrest of the disease. Even though such a result is highly exceptional in a large experience, it points clearly to the need for an open mind. Available evidence points strongly to the diverse etiology of so-called essential hypertension and it may well be that a neurogenic mechanism is the sole cause of hypertension in a small number of patients. Unfortunately these individuals cannot be recognized in advance of operation. Even in these rare instances it is not to be assumed that the disease is cured since it is not reasonable, in the present state of our knowledge, that sympathectomy eliminates the still unknown primary mechanism. However, in light of the basic assumption that elevated blood pressure is the sole and direct cause of vascular disease it may be

accepted, although without final proof, that prolonged lowering of the blood pressure is of therapeutic value. It should be emphasized again at this point that there is equally valid evidence to support the two alternative opinions, that vascular disease in the kidneys precedes and is independent of the hypertension and that vascular disease and hypertension are independent of each other and are concomitant effects of a still unknown humoral mechanism. If either of these latter hypotheses prove to be correct, it is obvious that reduction of the blood pressure level by sympathectomy can serve no useful purpose.

There can be little question that sympathectomy has a place in the ill defined program of treatment of hypertension, but in view of its tentative rationale it must be regarded as an experiment as yet unfinished. Those who accept sympathectomy with more or less enthusiasm are impressed with mass statistics on longevity or with alterations in specific manifestations of the disease such as relief of symptoms, lowering of blood pressure, diminution of heart size, reversal of abnormalities in the electrocardiogram and regression of papilledema. Mass statistics on longevity may be misleading in a disease with a variable and unpredictable course in which an adequate control is not available.

Relief of symptoms because of their subjective nature cannot with confidence be specifically ascribed to any particular therapy. Furthermore, it is common experience that subjective symptoms may be significantly relieved in patients in whom the blood pressure level is unaffected. The level of the blood pressure is dependent not only on the causative mechanism but upon numerous vasoconstrictor influences unrelated to the basic causative mechanism and subject to spontaneous recession. Thus partial recession of the blood pressure level may be accounted for by prolonged bed rest together with a resigned acceptance of the illness and the reassurance which results from intelligent application of simple psychotherapy. Reduction in size of the heart

cannot be accepted without reservation since in many published reports it is obvious that dilatation and heart failure were present before operation, as indicated by disappearance of x-ray evidences of pulmonary congestion, an effect which is often accomplished by prolonged bed rest alone. Reversal of electrocardiographic changes in the T waves is in the same debatable category since reversal of these changes has been reported after treatment with such apparently unrelated procedures as renal extract, tyrosinase, rice diet, sodium-free diet and after mercurial diuresis. The same reservation applies to papilledema. There are as yet no satisfactory data on the incidence of spontaneous reversal of these manifestations in an untreated control group of hypertensives.

Two patients in our series may be cited as examples of the difficulty in interpreting the results of sympathectomy: The first was a forty-five year old male whose preoperative blood pressure averaged 160/120 mm. Hg. His only preoperative complaint was substernal pain on effort. His preoperative electrocardiogram was normal. Following operation, his usual blood pressure was in the vicinity of 130/70 mm. Hg. He was under observation for eleven months postoperatively. During this period the anginal episodes continued without change and three months after operation he developed episodes of acute left ventricular failure. Repeated electrocardiograms during the period of normal blood pressure showed progressive inversion of the T waves in the first and precordial leads. In the eleventh postoperative month he died suddenly. It seems a fair conclusion from these data that the coronary disease in this instance progressed at the anticipated rate in spite of the absence of elevated blood pressure. The second patient was a thirty-eight year old white male who had established hypertension during a ten-year period of observation. At the time of sympathectomy his blood pressure was in the vicinity of 240/160 mm. Hg. His electrocardiogram showed the so-called hyper-

tension pattern of inverted T waves in the first and precordial leads with depression of the ST segment in lead I. There were fresh hemorrhages in the retinae with well marked blurring of the disc margins. He was in moderate chronic left ventricular failure. Following operation, his blood pressure level remained consistently at about the level of 160/100 mm. Hg. Six months after operation blurring of the discs had completely subsided and the T waves had returned to the upright position. However, one year postoperatively, and in spite of the apparent objective improvement of the blood pressure level, the electrocardiogram and the retinae, the patient developed for the first time repeated episodes of acute left ventricular failure and acute encephalopathy, characterized in various episodes by transient aphasia, hemiparesthesia and acute transient loss of vision. He is still alive four and one-half years after operation. It would appear that this patient, while showing regression in some manifestations of the disease, showed progression in others. One is confronted with obvious difficulty in arriving at a decision as to the usefulness of operation in this instance.

These case histories are cited not because they necessarily help to elucidate the problem but rather to indicate the latitude which is possible in interpretation. One could take the stand that in the first patient the operation was unsuccessful in preventing progress of the coronary disease in spite of normal blood pressure and in the second patient that the effect of sympathectomy cannot be interpreted with confidence; one might make the assumption that both patients lived for a longer period of time than might have been expected without operation. This problem is common and the discrepancies in the conclusions of various studies may well reflect a situation in which the same facts are subjected to different shades of interpretation.

Personal experience with sympathectomy has led us to the conclusion that as yet sympathectomy has not been shown to have

succeeded in significantly altering the course of hypertensive disease. However, there is reason to accept the possibility that if essential hypertension proves to be a disease of diverse etiology, a small segment of the hypertensive population may be materially helped by sympathectomy. It is the possible ultimate isolation of this small group from the large heterogeneous mass of so-called essential hypertensives which should sustain interest in the operation as a highly desirable clinical experiment.

SUMMARY

Good therapeutic effect in essential hypertension has been claimed for such diverse methods as salt restriction on the one hand, and sympathectomy on the other, to say nothing of thiocyanate therapy, psychotherapy and a host of others. Such an attitude toward treatment can lead only to the conclusion that none is adequate. This is quite understandable in view of the fact that the ultimate cause of hypertension is unknown and that all treatment at the present time is purely empirical.

Accepting this then as a fact, we have to define more closely our objective in treating persons with hypertension with our limited information. There appears to be a distinct division of opinion among those who believe that alleviation of subjective symptoms is a desirable objective and those who believe that lowering the level of blood pressure is a more desirable objective. It seems clear that subjective symptoms in hypertensive disease do not, with perhaps few exceptions, depend upon the level of blood pressure since it is a common observation that lowering of the blood pressure level by any means is not necessarily accompanied by alleviation of symptoms and that alleviation of symptoms may occur even when the blood pressure level has not been altered.

The ultimate goal of symptomatic measures is relief of subjective symptoms and while this is frequently accompanied by lowering of the blood pressure level, the latter is of secondary importance. Decline of blood pressure level is not to be inter-

preted as regression in the underlying cause of the disease, but rather as amelioration of those secondary and reversible factors which are superimposed on the basic causative mechanism.

While relief of subjective symptoms may completely rehabilitate a hypertensive patient, mere lowering of the blood pressure level without relief of symptoms serves no such purpose. This is not to imply that lowered blood pressure is necessarily without some benefit, but rather that it is not to be considered the prime objective of a plan of symptomatic management.

Perhaps the most valuable single device in rehabilitation of the hypertensive patient is psychotherapy; the planned and detailed methods employed by the psychiatrist are not necessarily superior to repeated conferences with a sympathetic physician who will give attention to problems responsible for emotional instability. A physician properly trained in general medicine and with an interest in psychiatry is competent to undertake such treatment and beneficial results are often obtained in a relatively short time. Simple, sympathetic reassurance is often sufficient to relieve disturbing symptoms. The physician can foster this attitude by prolonging the interval between examinations, particularly in the early uncomplicated period when symptoms are few or absent. Psychotherapy intelligently applied often results in dissipation of the anxiety, depression and irritability which accompany the phobia of high blood pressure.

Apart from elimination of the cause of the disease, which is not possible at this time except in rare instances, it would appear that the main objective of treatment should be to retard or prevent development of vascular disease which is the ultimate cause of disability and death. No significant progress has been made in this direction.

It is our present considered opinion that with rare exceptions any treatment based upon the assumption of similarity between experimental and human hypertension is doomed to failure. And, furthermore, that

any treatment directed solely toward temporary reduction of blood pressure is futile. Final treatment will come only when the causative mechanism of human hypertension is discovered and specific measures are devised for its elimination.

Except for the rare instance of pheochromocytoma of the adrenal and the very rare instance of unilateral renal disease, hypertension is not curable. The methods of treatment discussed in this seminar and others not touched upon are merely designed to alter the clinical aspect of hypertensive disease either by eliminating subjective symptoms or by lowering blood pressure. When both can be accomplished, patient and doctor are lulled into a sense of security, but whether or not any of the measures of treatment now at hand actually retard the progress of hypertensive disease is extremely doubtful. In spite of this pessimistic attitude toward present day treatment for hypertension and with full knowledge of what it means to the worried patient and the equally worried doctor, it would appear to be a healthier attitude and more likely to lead to ultimate solution than an attitude of ready acceptance which has the potentiality of engendering a false sense of security.

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Congenital Heart Disease

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DICKINSON W. RICHARDS, JR.: This clinic is designed to present both the surgical and physiologic aspects of some of the problems relating to congenital heart disease. Dr. Langmann will initiate the discussion.

DR. ALFRED G. LANGMANN: Although congenital heart diseases, or perhaps more properly congenital anomalies of the heart and great vessels, constitute only about 2 per cent of the total incidence of organic heart disease and about 5 per cent of that encountered in children, they have become a subject of particular interest and importance in recent years. Stimulation of this interest was due largely to the successful ligation by Gross in 1939 of a patent ductus arteriosus in a young girl. Since then operations for the correction or alleviation of three other cardiovascular anomalies have been introduced, viz., coarctation of the aorta, the tetrad of Fallot and 'vascular ring.'

The correct diagnosis of these anomalies which are amenable to surgical operation and of others for which corrective procedures may be devised in the future presents a real challenge, particularly to the clinician, the cardiologist, the physiologist and the roentgenologist. Roentgenograms of the heart taken at different angles and also esophograms have given valuable information about the size of the various chambers of the heart and abnormal partitions of the great vessels. In some medical centers angiocardiology has been found to be of distinct aid in the visualization of septal defects, the pulmonary circulation and the great vessels. Cinecroentgeno-

graphic study of the heart and great vessels promises to yield even more important data, especially in the province of dynamics. The successful catheterization of the heart, recently carried out even in infants, has furnished information of distinct value in the diagnosis of shunts of various types through the oxygen and blood pressure values so obtained.

Criteria have been set up for the clinical diagnosis of a number of congenital cardiovascular anomalies but it is well to remember that as further anatomic studies are made these criteria may have to be amended. A case in point is the 'machinery' murmur associated with patent ductus arteriosus. This still constitutes the most characteristic feature of the physical findings in this anomaly but is no longer considered a *sine qua non*; for a fair number of patients have been operated upon in whom a patent ductus was found but who before operation had only a systolic murmur although they had other features suggestive of this abnormality.

It is generally stated that about 50 per cent of patients with congenital cardiovascular anomalies have lesions that are clinically insignificant. Accurate anatomic diagnosis is rendered all the more difficult by the fact that in many instances the anomalies are multiple. The most severe of these, often associated with extreme cyanosis, are encountered in early infancy and are compatible with but short life. In the children who survive, every attempt should be made to arrive at as accurate an anatomic diagnosis as possible. Age is an

important factor if surgery is to be considered. It seems to be generally agreed that children tolerate intrathoracic interference better than adults and that they make a quicker recovery after operation. The decision as to whether or not surgical intervention is indicated if symptoms are absent or minimal is a matter that must be decided in each individual case.

DR. RICHARDS: Dr. Humphreys will present the surgical aspects of patent ductus arteriosus.

DR. GEORGE H. HUMPHREYS II: In the past nine years forty-nine patients with the presumptive diagnosis of patent ductus arteriosus have been operated upon at the Columbia-Presbyterian Medical Center. Of these eleven proved to have some other anomaly. Of the thirty-eight patients in whom a patent ductus arteriosus was present, in twenty-six the ductus was uncomplicated by other anomalies or by superimposed infection and was ligated (twenty-two cases) or divided and sutured (four cases) with complete recovery. Four of the twenty-two patients in whom ligation was performed have persistent murmurs which raise the question of recurrent patency although in one case recurrence has been proved by cardiac catheterization not to exist. All four patients in whom the ductus was sutured are free of murmur.

Six of the patients operated upon were suffering or had suffered from subacute bacterial endocarditis. Three had received no penicillin and were actively infected at the time of operation. Two of these are cured and free of murmurs six and five years, respectively, after operation. The third died one month after operation following drainage of a metastatic brain abscess; at autopsy the ductus was closed and the vegetation on the pulmonary artery had healed. One patient was apparently cured by penicillin and his ductus subsequently divided with complete recovery. Two patients developed recurrences; one was cured of both the infection and the recurrence by subsequent ligation and is well and free of murmur six years later;

the other was apparently cured of the infection by penicillin, was then re-operated upon and an aneurysm divided and sutured. She is well two years later.

Two additional patients developed recurrence following ligation. One had an aneurysm of the pulmonary artery at the time of ligation and only one ligature was used. Her murmur never disappeared and it is assumed that the ligature cut through. Recurrence with aneurysm occurred in one otherwise uncomplicated case with death a year later following wiring of the aneurysm.

In addition to the two deaths mentioned there were four other patients with patent ductus arteriosus who died after operation. One with an uncomplicated ductus died of hemorrhage on the operating table during an attempt to divide and ligate the ductus; a death which would not have occurred had ligation only been performed. One patient was a middle aged hypertensive in borderline cardiac failure. Operation was done in the hope of relieving her cardiac load but she died in failure three weeks after operation. In one patient the ductus formed part of a more complicated anomaly resulting in a vascular ring around the trachea and esophagus; death from left heart failure followed division of the ductus. The sixth death occurred of circulatory failure on the operating table following exploration only. At autopsy a patent ductus complicated by a large dissecting aneurysm of the pulmonary artery due to subacute bacterial endarteritis was found.

Thus the total mortality of six patients, or 16 per cent, was due largely to complications of the disease. In only two, or 5 per cent, was it due directly to the operation. Thirty-two patients, or 84 per cent, recovered from operation and only one (in whom the operation was technically inadequate) has convincing evidence of persistent patency.

I should like at this point to introduce Miss W., one of our patients who illustrates many points of interest. She is a young lady who has been known to have a cardiac murmur since infancy. During childhood

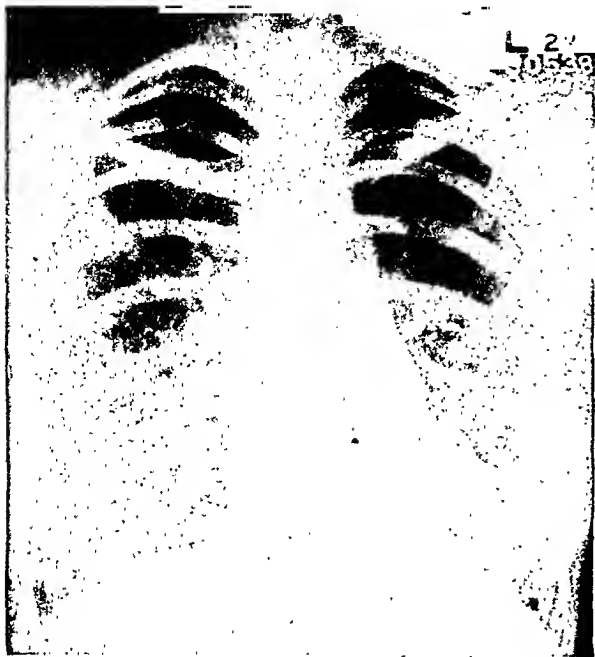


FIG. 1. X-ray of heart of Miss W., with patent ductus arteriosus, showing increase in transverse diameter of heart and prominence in area of pulmonary artery.

an attempt was made to have her restrict her activity because of the murmur but she herself never experienced any inability to carry out normal exercise. She grew and developed at a normal rate. She did not present a feeding problem. She had no abnormalities of growth. In fact she was unusually free of any serious illness.

During her adolescence she was supposed to continue her restrictions but frequently disregarded them and felt no ill effects. For example, when she went to high school she was supposed to take the elevator, but she often climbed four or five flights of stairs without dyspnea. She stated that she had no cardiac symptoms of any kind. Since graduating from high school she has worked in a department store.

I saw her first last summer. She looked much as she does now, a healthy young woman with no cyanosis, no clubbing of fingers or toes and no abnormal pulsations in the nail beds at rest. On the examining table the cardiac pulsation was not unusually strong. There was a slight thrill felt over the base of the heart. A loud, continuous, rough murmur was present and was heard most clearly over the third

left interspace. The pulmonic second sound was greatly exaggerated. The murmur was transmitted to the apex of the heart and heard over the aorta posteriorly and over the femoral artery. The blood pressure was 155/53. There was a considerable increase in the pulse pressure but there were no other abnormalities.

She was admitted September 19th and studied by Dr. Baldwin whose findings will be presented later. At the time of her admission her blood pressure was the same as when previously seen. Her hemoglobin was 14 Gm. The red count and the hematocrit were normal. The electrocardiogram was normal except for unusual Q_2 and Q_3 which made Dr. Wégria, who was not informed of the diagnosis, raise the question of a congenital defect. X-ray of the heart (Fig. 1) showed a slightly increased overall diameter of the heart as compared to the normal. There was a slight prominence, not very conspicuous, in the pulmonary area and otherwise very little except for some increase in the bronchovascular markings of the lung.

We believed that with this increase in the heart size, with the high pulse pressure, and particularly after the catheterization studies, her heart was unquestionably carrying a burden from which it could be relieved. She was therefore operated upon on September 27th. A ductus about $1\frac{1}{2}$ cm. long and 1 cm. in diameter was present in its characteristic anatomic position. The pulmonary artery was considerably dilated, more than one would suspect from the x-ray picture, and it overlay the arch of the aorta. The ductus was ligated in continuity with three ligatures of umbilical tape; the thrill disappeared immediately. Her recovery was without complication. The blood pressure rose to 125/90 on the second day postoperatively and then fell gradually to 110/80 where it has remained. She was out of bed on the second day after operation and she went home on the ninth day after operation. During the six weeks after operation she gradually returned to normal activity. She noted no subjective

change in the heart, but when I saw her six weeks later stated that she felt lighter and that her extremities no longer tended to be cold and uncomfortable. It is a common finding that the peripheral circulation is improved in such cases.

Her pulmonic second sound remained somewhat accentuated but there was no murmur whatever. The postoperative x-ray taken at that time showed the prominence in the pulmonic area still present. That is not surprising; when the pulmonary artery has been dilated for many years, it does not shrink immediately. The bronchovascular markings in the lungs were now normal and the transverse diameter of the heart was obviously less.

DR. RICHARDS: Before Dr. Greene gives the measurements in the case of Miss W. I might go over briefly some of the procedures by which we attempt to gain physiologic information in cases of this kind. Actually the measurements that are made are not very many and are quite simple in principle. They involve, of course, catheterization of the right side of the heart, including right auricle, right ventricle and, when possible, the pulmonary artery. Occasionally, if there are defects, the catheter may go into other places. The chief criteria for diagnosis are alterations in oxygen content in one or another of these chambers and alterations in pressures. By means of these measurements the anatomic lesions in a good many instances can be quite well defined.

From the point of view of diagnosis the most simple anatomic lesion is that of interventricular septal defect. In this condition oxygenated blood is forced from the left into the right ventricle during cardiac systole. The oxygen content of the right ventricular and pulmonary arterial blood is increased as compared with that of the right auricular blood. The pressure in the right auricle is normal. The right ventricular pressure is increased to a variable extent; it is usually significantly elevated if the septal defect is sufficiently large, by reason of the left ventricular pressure being trans-

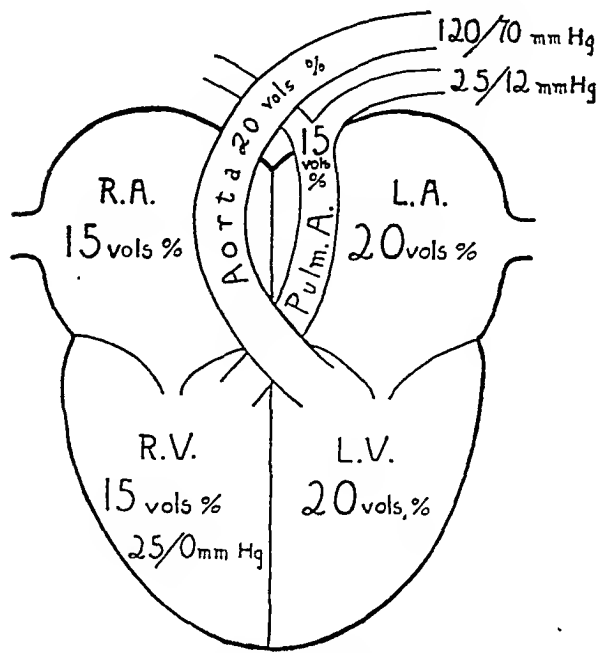
mitted, in part, to the right side. If the right ventricular pressure is increased, then that in the pulmonary artery is also increased. These are the findings associated with an interventricular septal defect.

If there is a communication between the aorta and pulmonary artery, then oxygenated blood flows from the aorta into the pulmonary artery and the oxygen saturation is increased in the pulmonary artery. If the pulmonary valve is competent, the right auricular and right ventricular oxygen saturations remain normal. As for the pressures they are not greatly different from those found in interventricular septal defect. The increased flow from the high pressure aorta into the lower pressure pulmonary artery usually increases pulmonary arterial pressure to some extent and the right ventricle must hypertrophy to meet and overcome this increased pulmonary arterial pressure.

In evaluating the phenomenon of increased ventricular or pulmonary arterial pressures there are two factors to be considered: one is that of obstruction and the other is that of increase in flow. In the instances just cited, increase in flow is associated with some increase in pressure. In other conditions, such as pulmonary artery narrowing or stenosis, the increase in pressure occurs with a lessening of flow. It therefore becomes very important to quantitate the actual blood flows in any given case, and that can be done quite readily by the so-called Fick principle. This can be described briefly as follows:

If one obtains (Fig. 2) a figure of 20 volumes per cent of oxygen in the arterial blood by actual measurement, that means that there are 20 cc. of oxygen contained in each 100 cc. of arterial blood. If one obtains from the right auricular (or venous side) a figure of 15 volumes per cent, that means 15 cc. of oxygen per 100 cc. of venous blood. We also measure the total oxygen used by all the tissues in a minute's time. For example, it is 300 cc. per minute; then knowing that for each 100 cc. of blood flowing from the arterial to the venous side

5 cc. of oxygen are taken up by the tissues and that the total oxygen taken up by the whole body in a minute's time is 300 cc., then 300 divided by 5 will give the total number of batches of 100 cc. each of blood flowing from the arterial to the venous side,



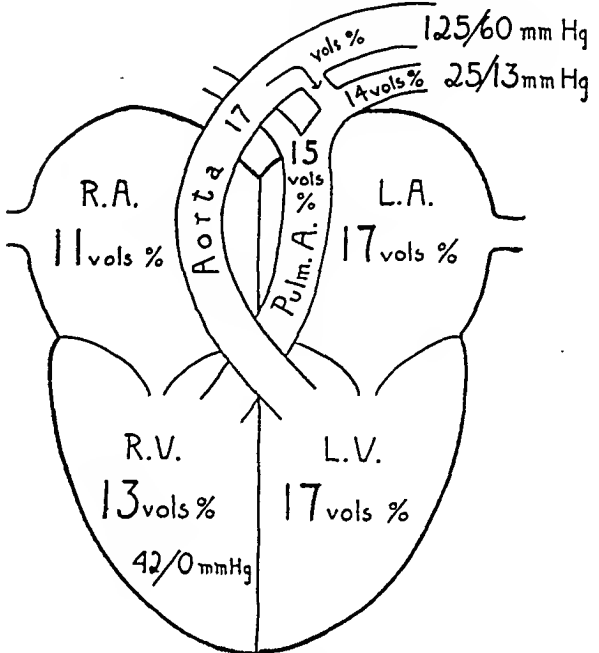
Pulmonary blood flow = $\frac{300}{20-15} \times 0.1 = 6 \text{ L./min.}$
Systemic blood flow = $\frac{300}{20-15} \times 0.1 = 6 \text{ L./min.}$
Arterial saturation at rest = 96%
Arterial saturation after exercise = 96%
Hemoglobin = 15 Gm.
Hematocrit = 45%

FIG. 2. Showing the oxygen saturation and pressure relationships in a normal individual. The blood flow [figures are in terms of liters per minute.

or the total systemic blood flow. In this case it would be sixty batches of 100 cc. each, or 6,000 cc. of blood flow per minute. The smaller the oxygen difference from the arterial to the venous side, the less oxygen is taken up by the tissues per unit of blood flowing. That means the faster the blood flow and the greater the total volume flow per minute.

In the lungs the same operation obtains, with the oxygen, of course, going into the blood instead of coming out. But the same principle enables one to measure the total blood flow through the lungs. If one obtains blood from the pulmonary artery and

finds, for example, 15 cc. of oxygen per 100 cc. of blood, and in a brachial or femoral artery (which is usually the same as the pulmonary vein) it is 20 cc., that means that 5 cc. are added to each 100 cc. of blood flowing through the lungs. The



Pulmonary blood flow = $\frac{240}{17-14} \times 0.1 = 8 \text{ L./min.}$
Systemic blood flow = $\frac{240}{17-11} \times 0.1 = 4 \text{ L./min.}$
FIG. 3. Illustrating the derangement in oxygen saturation and pressures in Miss W., with patent ductus arteriosus.

pulmonary blood flow in this instance (Fig. 2) would be 6,000 cc. per minute.

With this brief introduction Dr. Greene will give the results in the case just presented by Dr. Humphreys, the case of Miss W.

DR. DAVID G. GREENE: Figure 3 presents the data that we found in studying the first patient. We wanted to know the size of the shunt and thus the resultant extra burden on the heart. As the patient was asymptomatic we hoped that this information would help Dr. Humphreys in making the decision whether or not to operate.

The oxygen content of the mixed venous blood in the right auricle was 11 volumes per cent. The right ventricular blood oxygen content was higher, 13 volumes per cent,

indicating some admixture of arterialized blood in this chamber. At the bifurcation of the pulmonary artery, close to the site of a possible patent ductus, we obtained blood with a still higher oxygen content, 15 volumes per cent, indicating further oxygenation of the right ventricular blood. The catheter tip may have been almost directly in the stream of arterial blood coming from the aorta. Further out in the left pulmonary artery there was a blood oxygen content of 14 volumes per cent, probably a more representative value for the mixed pulmonary artery blood.

We leave for a moment the question of the site of the shunt to calculate its size. We assume that the femoral arterial sample represents the blood in the aorta, the left ventricle, the left auricle and the pulmonary vein. Using this oxygen content, 17 volumes per cent, and the pulmonary artery oxygen content of 14 volumes per cent, we find a pulmonary arteriovenous oxygen difference of 3 volumes per cent. The oxygen consumption measured at the same time was 240 cc. per minute. Dividing the oxygen consumption by the pulmonary arteriovenous difference gives a pulmonary blood flow of 8 liters per minute. Calculating in the same manner but using the femoral artery oxygen content, 17 volumes per cent, and the right auricular mixed venous blood oxygen content, 11 volumes per cent, a systemic arteriovenous difference of 6 volumes per cent is obtained. This value divided into the oxygen consumption per minute gives a systemic blood flow of 4 liters per minute. Therefore, the pulmonary blood flow of this patient is twice her systemic blood flow, an excess circulation which must represent a considerable burden on her heart. Additional evidence of increased cardiac work is the significantly elevated right ventricular systolic pressure of 42 mm. of mercury.

The question of the location of the shunt or shunts cannot be settled from the blood oxygen data alone. In this instance there were two possibilities to be considered: an interventricular septal defect plus a patent

ductus, or a patent ductus with regurgitation of oxygenated blood through an incompetent pulmonic valve. The latter interpretation was indicated by the finding of a dilated pulmonary artery at operation and the disappearance of the murmur following surgery. We have encountered pulmonic regurgitation in one other patient who at operation was found to have a patent ductus; however, three other patients with a large ductus had competent pulmonic valves.

DR. RICHARDS: I might say that in resolving the question of pulmonic regurgitation, re-study after operation will sometimes give the answer. If there has been pulmonary regurgitation and the ductus is shut off, with normal relations re-established, the regurgitation will sometimes be overcome, the pulmonary artery will resume its normal size and the pulmonary arterial and right ventricular oxygen will become normal. Whereas if there is a septal defect that is not corrected by operation, some oxygen admixture will persist after operation.

Dr. Cournand has carried out one study in a case of patent ductus arteriosus before and after operation in which this type of admixture did disappear following operation, showing that it was due to pulmonary regurgitation and not to a septal defect.

DOCTOR: You have not catheterized this patient a second time?

DR. RICHARDS: No.

DR. HUMPHREYS: It would be nice if all cases were as simple as that of Miss W. But they are not, and we will try to present not only established and clearcut situations but also those which remain in doubt. In these particularly the surgeon is now following the physiologist and relying on him very heavily to elucidate what is going on and to give him a lead as to what sort of mechanical change might help the patient.

I would like now to present another patient, a child in whom we were not able to get cardiac studies. This child was born in March, 1941, in Sloane Hospital, the second child of American parents. There was a normal delivery and normal background.

He was well developed at birth, had good color, good nutrition and no difficulty in breathing. Unfortunately, his heart was not examined before he was discharged at the age of ten days. He re-appeared six months later, referred back by the Health Clinic because of bronchitis, failure to gain weight and 'blue spells' associated with crying. Examination in the clinic showed poor nutrition, cardiac enlargement and a low pitched systolic murmur over the precordium, maximal at the left sternal border. X-ray confirmed the cardiac enlargement and showed some congestion in the lungs. He was followed closely in the clinic. It was thought that no cardiac diagnosis could be made although the question of patent ductus arteriosus was raised. During the six months he gained only 1 pound and at the end of a year weighed 11 pounds. He was eating poorly, had an almost constant cough and respiratory difficulty. X-ray at one year revealed that the heart had increased in size in the intervening six months and now showed a clearcut bulge in the region of the pulmonary artery.

With this finding, and in spite of the fact that the murmur was still systolic and in spite of the fact also that the child was in very poor shape, it was believed that a diagnosis of patent ductus was sufficiently well founded to warrant operation; it was thought furthermore that his poor progress was such that he would very likely die if nothing were done and that the risk of operation should be taken.

At operation on April 9, 1942, a large ductus was found and doubly ligated after entering the pericardium. Postoperatively his condition was poor for the first week, with both circulatory and respiratory symptoms. He had a definite pneumonia which was helped by sulfadiazine but he then developed a sulfadiazine reaction; the drug had to be stopped whereupon the pneumonia recurred, but eventually his temperature returned to normal and by the end of the second week his condition already appeared better than before operation. He remained in the hospital for sixty-one days

and during this period he made such a rapid improvement in weight and strength that his weight on discharge was 19 pounds, almost twice his admission weight.

After removal of the dressing a persistent, soft systolic murmur was heard over the apex and on discharge this murmur had increased in its area to include the whole left border of the heart. This, of course, immediately raised the question as to whether the ductus had been completely occluded, whether one of the ligatures had cut through, or whether he had some other anomaly. He has been followed now for five years after the operation. This murmur has been consistently present. It has varied in intensity from visit to visit, at times being quite rough and accompanied by a thrill, at other times (as at present) much softer and located lower over the heart.

During the first two years weight and growth gain were spectacularly good. During this period his cardiac shadow improved and his electrocardiogram, which before operation had shown not only left preponderance but also inverted T waves suggesting myocardial damage, returned to normal. His x-ray pictures in 1943 (at the age of one and one-half years) and in September, 1944 and the spring of 1945 have changed very little; they are still abnormal. The heart is more to the left than it should be. There is still a prominence in the pulmonic area although not as pronounced as preoperatively. On the other hand his pulmonary fields are much better than before operation. Recently his weight gain has slowed down. He has had a number of infections. He appears less well than he did two years ago although he is growing normally. In December of last year, for the first time, definite cyanosis and slight clubbing were noted in the clinic. The question arises as to whether this child with his persistent murmur (not recurrent, he has never been free of a murmur) and with these findings does not also have other difficulties.

The third case (G. G.) is that of a child in whom cyanosis was noted at the age of two months. At two years he suffered a

fractured skull following which he developed a hemiplegia which has left some residual weakness. His growth and development, however, were not delayed. His nutrition was reasonably good, although not excellent, but by the time he was four or five years old he began to develop exertional dyspnea which became more pronounced as he grew and attempted more exercise. After exercise cyanosis became more prominent; at rest it was much less but still noticeable.

He was admitted to Babics Hospital on March 8, 1946, at the age of eleven years. He showed definite cyanosis of the lips and nail beds with marked clubbing of fingers and toes. There was a slight residual weakness of the extremities on the right. Heart examination showed some bulging of the precordium with no visible pulsation, thrill or shock. There was no enlargement of the heart to percussion, the sounds were regular and of good quality. A loud, harsh murmur was heard throughout systole in the aortic area transmitted throughout the precordium but not to the back.

X-ray (Fig. 4) revealed a small cardiac silhouette and large hilar shadows with approximately normal bronchovascular markings. This picture is not typical of pulmonic stenosis, which is characterized by a marked defect in the area of the pulmonary artery, diminished or faint vascular markings and a rising of the apex of the heart above the diaphragm.

This child was operated upon in May, 1946. The end of the right subclavian artery was anastomosed to the side of the small right pulmonary artery by suture. This is the operation described by Blalock. It has, as you see, formed a surgical patent ductus. In other words, we created in this child what we eliminated in the other patients. He made an uncomplicated recovery and was allowed up after the third day.

Before operation his hemoglobin was 19 Gm. with a red count of 11,500,000. The hematocrit was 66, an increase of 40 per cent. Three months after operation his hemoglobin had fallen to 13 Gm. and his

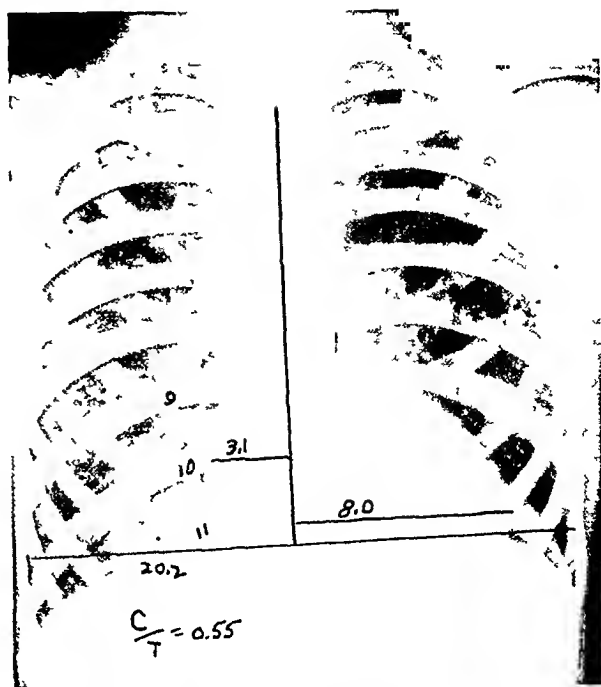


FIG. 4. Preoperative x-ray of the heart in G. G. The transverse diameter is not increased.

red count to 5,800,000. His arterial saturation before operation was 72 per cent at rest. Three months after operation it was 89 per cent. This child went home after the second week and during the next three months he did extremely well. His cyanosis became imperceptible and it no longer appeared on exercise. In fact he rejoiced in his ability to exercise to the point that when he returned to school in the fall he joined the football team and played very vigorously.

On November 5th he was re-admitted to the hospital following attacks of vomiting, headache and low grade fever which had begun about four weeks previously. This worried us because of the possibility of subacute bacterial endocarditis. Especially was that in mind since examination at that time showed him as you see him now, with no obvious cyanosis but with some clubbing still persisting although now very largely disappeared.

At that time his heart (Fig. 5) was greatly enlarged and overactive. The loud, rough systolic murmur was still present and in addition there was a continuous murmur in the operative area. His hemoglobin on admission was 13.5, the red count 5,000,000

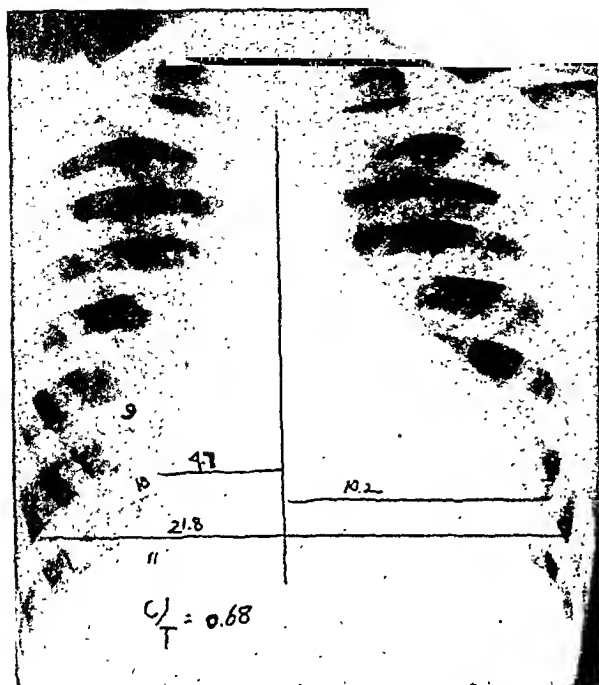


FIG. 5. Postoperative x-ray of heart in G. G. showing marked increase in size following the surgical establishment of a patent ductus equivalent.

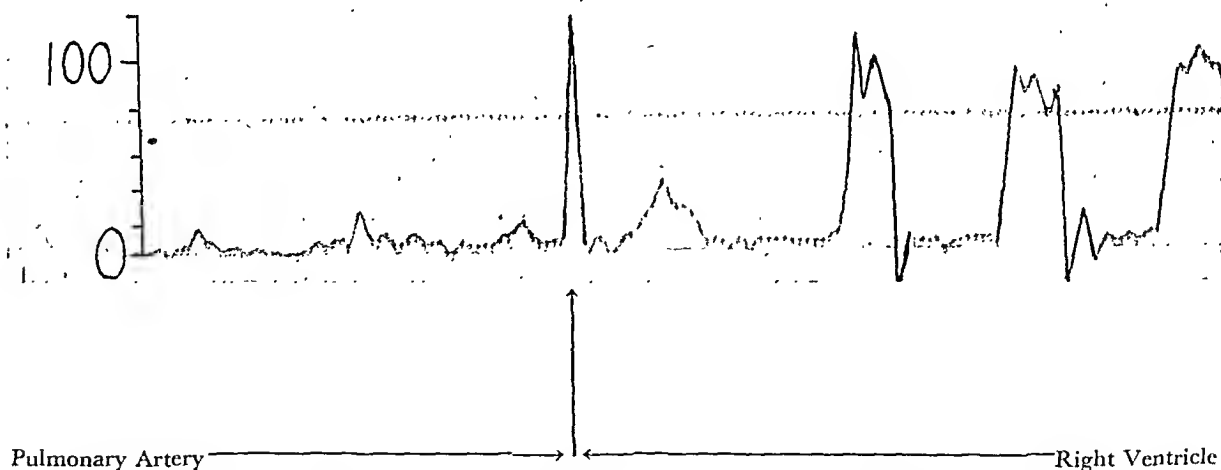


FIG. 6. Pressure tracing from pulmonary artery and right ventricle of patient with tetrad of Fallot.

and the oxygen saturation 88 per cent. His electrocardiogram showed an increase in the P-R interval but otherwise it was not changed. His blood cultures were repeatedly negative. His fever after a week of irregular elevation dropped to normal without any antibiotic treatment and after a week he was allowed to go home. Since that time how has he been?

MOTHER: Fine.

DR. HUMPHREYS: He has not had any more attacks?

MOTHER: He has headaches but they last only a day and then are gone. He has no more diarrhea, no more vomiting or fever.

DR. HUMPHREYS: He is still able to get around pretty well?

MOTHER: He does everything.

DR. HUMPHREYS: Thank you very much.

DR. RICHARDS: This patient has been studied and followed very carefully by Dr. Baldwin. Would you tell us about your work, Dr. Baldwin?

DR. ELEANOR DEFOREST BALDWIN: The diagnosis of pulmonic stenosis can be made by passing a catheter into the right ventricle and pulmonary artery and measuring the pressures. In the right ventricle the systolic pressure is greatly elevated while in the pulmonary artery beyond the stenotic area the pressure is low and the pulse pressure small. This is well demonstrated in pressure tracings from a patient with the

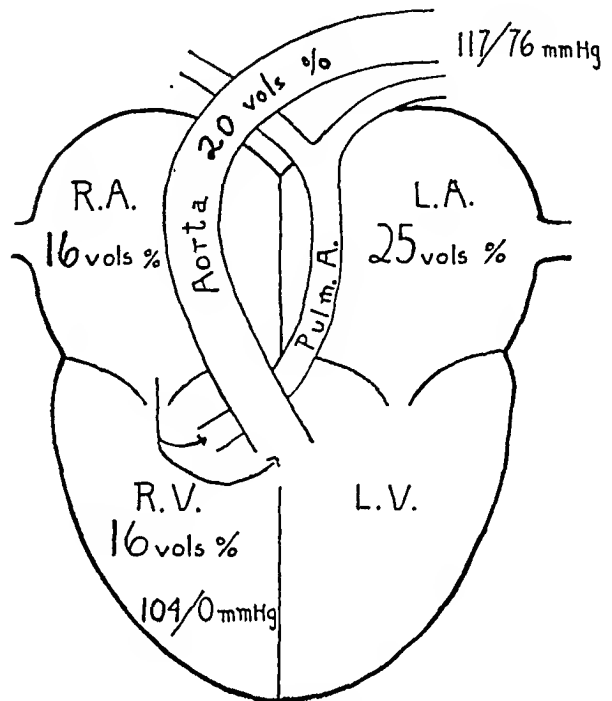
tetrad of Fallot. (Fig. 6.) The pulmonary artery pressure is only 19/10. On withdrawal of the catheter tip into the right ventricle a much higher pressure, 102/3, is immediately recorded. As frequently happens with this maneuver there are a few abnormal contractions as the catheter tip enters the ventricle.

In case G. G., just presented by Dr. Humphreys, observations made during catheterization of the right heart are typical of the physiologic changes found in cases of

interventricular septal defect associated with pulmonic stenosis: (1) The systolic pressure measured in the right ventricle is very high, approximately that of the peripheral arterial system. In this case (Fig. 7) the right ventricular systolic pressure was 104 mm. of mercury, corresponding closely to the systolic pressure of 117 which was obtained simultaneously in the femoral artery. (2) The pulmonary blood flow is considerably less than the systemic blood flow as calculated by the Fick formula from the minute oxygen consumption and oxygen arteriovenous differences.

We have direct measurements from which we may calculate the systemic blood flow. Using these figures, we find that the oxygen arteriovenous difference between the aorta and right auricle is 20 minus 16, or 4 volumes per cent. The minute oxygen consumption of this patient during the blood sampling was 172 cc. The systemic blood flow is 172 divided by 4, or 4.3 liters per minute. Since we did not obtain the oxygen content of either the pulmonary artery or vein, certain assumptions must be made to estimate these values. The pulmonary vein and left auricular blood oxygen content is taken to be 25 volumes per cent with a 96 per cent oxygen saturation. This figure is chosen because we have found that blood obtained directly from the pulmonary vein in patients with interauricular septal defects has an oxygen saturation between 94 and 96 per cent; and our assumption is therefore valid if pulmonary function is normal and blood is aerated well in flowing through the lungs. If we assume further that the pulmonary artery contains blood similar in oxygen content to that in the right ventricle, the pulmonary oxygen arteriovenous difference is 25 minus 16, or 9 volumes per cent, which divided into the oxygen consumption of 172 cc. gives us a pulmonary blood flow of only 1.9 liters. However, as we will show in the next case, the pulmonary artery may receive systemic blood from a patent ductus or bronchial arterial anastomosis. If only such blood were circulating through the lungs, the

pulmonary arteriovenous difference would be 25 minus 20, or 5 volumes per cent, and the pulmonary blood flow 3.4 liters. This maximum for pulmonary blood flow is still less than the systemic blood flow. Since the pulmonary blood flow is mechanically



$$\text{Pulmonary blood flow} = \frac{172}{25-16} \times 0.1 = 1.9 \text{ L./min.}$$

$$\text{Systemic blood flow} = \frac{172}{20-16} \times 0.1 = 4.3 \text{ L./min.}$$

Arterial saturation at rest = 75%

Arterial saturation after exercise = 45%

Hemoglobin = 19 Gm.

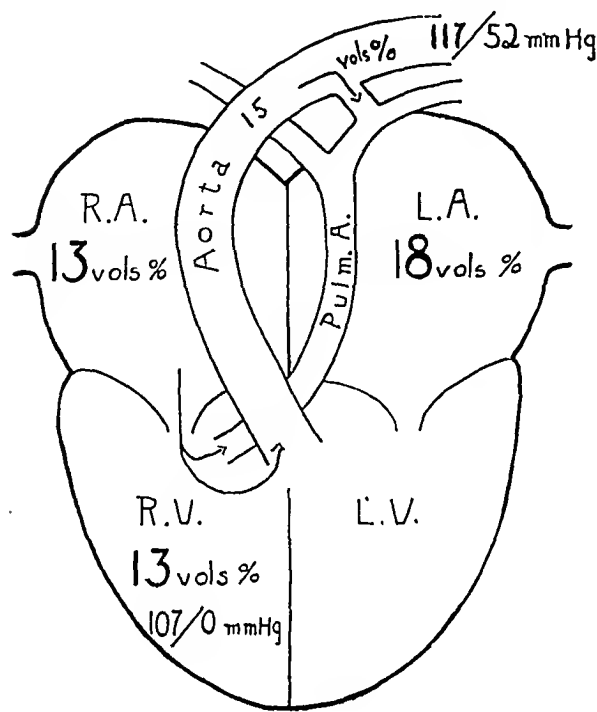
Hematocrit = 66%

FIG. 7. Indicating the abnormal findings in G. G. before operation. These represent the tetrad of Fallot.

limited by the stenosis, the volume of blood flowing through the shunt would be expected to increase under conditions which augment the volume of blood returning to the right heart. A measure of the extent of this increase is the profound drop of arterial oxygen saturation, from 75 to 45 per cent, observed in this patient following the very mild exercise of walking up and down a step twenty times during one minute.

Following his operation, during which the subclavian artery was anastomosed to the pulmonary artery, we repeated our

studies. (Fig. 8.) The right ventricular systolic pressure was found to be unchanged, 107, 0 mm. of mercury. The femoral arterial pressures were 117/52 mm. of mercury; the systolic identical with that observed before operation, the diastolic lower by 20 mm.



Pulmonary blood flow = ?
Systemic blood flow = $\frac{168}{15-13} \times 0.1 = 8.4 \text{ L./min.}$
Arterial saturation at rest = 86%
Hemoglobin = 13.4 Gm.

FIG. 8. Postoperative findings in G. G. To the tetrad of Fallot has been added a patent ductus.

of mereury. (It is of interest that the pulse pressure increased in this subject in whom an arteriovenous fistula was created, whereas it decreased in the preceding patient following the ligation of the patent ductus.) The oxygen contents of the right auricular and ventricular bloods are again identical with one another, 13 volumes per cent, representing an oxygen saturation of 75 per cent. The blood leaving his left ventricle has an oxygen content of 15 volumes per cent and an oxygen saturation of 86 per cent. His systemic oxygen arteriovenous difference is 2 volumes per cent. Since his minute oxygen consumption is unchanged from the preoperative value of 172 cc., the systemic

blood flow is 8.4 liters a minute. The catheter could not be passed into the pulmonary artery so it was impossible to measure the pulmonary blood flow. Nonetheless, the rise of the resting arterial saturation to 86 per cent indicates that there is a greatly increased flow of blood through the artificial patent ductus.

Obviously the operation has not changed the dynamics within the right ventricle; the pulmonic stenosis and right to left shunt into the over-riding aorta exist as before. However, the additional blood flow through the lungs by way of the anastomosis increases the volume of arterialized blood returning to the left heart, raising the saturation of the blood leaving the left ventricle from 75 to 86 per cent. This means that there has been an increase of the oxygen tension in the arterial blood from 39 to 86 mm. of mercury. The saturation of the mixed venous blood is now 75 per cent, which is identical with the saturation of his preoperative arterial blood. The larger amount of oxygen available to the tissues of the body accounts for this boy's spectacular improvement following operation.

The increased systemic blood flow observed postoperatively raises an interesting question. The identical oxygen consumption, measured during the two procedures eliminates an increase in the metabolic demands of the body as a cause. An increase in the cardiac output is the common finding in cases of arteriovenous shunts elsewhere in the body and is considered to be a compensating mechanism. The decreased viscosity of the blood of this patient, as evidenced by the drop of his hematocrit from 66 per cent to normal values, may in addition contribute to the postoperative increase of his systemic blood flow.

DR. ANDRÉ COURNAND: We have seen a case which was quite similar to this one before operation, in which we could demonstrate definitely a shunt from the right to the left on slight exercise.

DR. RICHARDS: Are there other questions?

DR. ROBERT F. LOEB: I should like to ask about left ventricular hypertrophy in

this boy. It is obvious that what we do in this operation of Blalock's is to induce an anomaly which we rectify in people who do not have worse trouble. The question that has been in my mind is: how long will it be before we find that these patients, who have been relieved of cyanosis and have improved function temporarily, run into difficulties such as are encountered with any large functioning patent ductus? This child has developed definite cardiac hypertrophy and I should like to know how often this occurs. How long a period of time elapses before it does occur?

DR. RICHARDS: The 8.4 liters per minute indicates a real increase in the systemic blood flow. When venous communication occurs suddenly from traumatic causes, cardiac hypertrophy develops quite rapidly if the communication is large.

DR. HUMPHREYS: X-rays of this boy showed a good deal of cardiac dilatation. It should be emphasized that he had overexerted himself. He is a good case to show because he does bring up exactly the point made by Dr. Loeb. We are creating in these children all the liabilities which we are eliminating in such patients as we showed first. This child does have an increased load on the heart and does have as much, maybe more, risk of bacterial infection. That risk is one which is considered worth while taking for the sake of the immediate relief, which is very dramatic.

DR. JOHN CAFFEY: In our roentgenologic follow-up studies, this boy is the only patient who has shown cardiac enlargement following operation. We have four other good follow-ups and there has not been even a transitory dilatation of the heart. It is not part of the operation but something in this patient.

DR. BALDWIN: A factor in this may be that several of the patients have had a hemiplegia. This patient felt so well on being suddenly released that he overexerted himself.

DR. RUSTIN McINTOSH: I would like to ask about the postoperative regimen in that connection. It is customary to let children

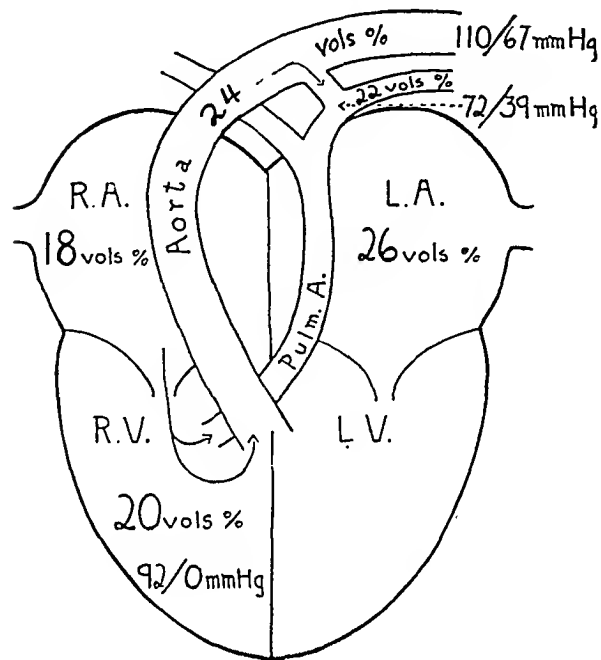
with malformation of the heart find their own level of exercise tolerance. Do you believe it would have made any difference at all if his exercise had been restricted by directives following operation, or do you think that it is a case of six of one and half a dozen of the other and let him go and play football?

DR. RICHARDS: I think a certain amount of protection would be a good thing. I do not know how others feel about this point.

DR. McINTOSH: One could argue that it is a question of the speed of development. The same change can be effected, that is, the same degree of cardiac dilatation and hypertrophy might be reached at a later time if the daily exertion were less.

DR. BALDWIN: The next case (D. F.) shows the importance of catheterizing the pulmonary artery whenever possible to avoid missing important anomalies. He is a twenty-two year old Bermudan who has been blue since birth. His growth was slow and his activity somewhat limited. He was, however, able to ride a bicycle, an important activity in Bermuda, and in recent years has worked as a barber. For twelve months before his trip to the States he suffered a series of hemoptyses, two of which were alarming and during which he is said to have lost at least 1 pint of blood. On arrival here he denied extreme limitations of his activity. He was able to climb two flights of stairs slowly but not rapidly. He was cyanotic with marked clubbing of the fingers and toes. His heart was enlarged, both to the right and to the left. A loud systolic murmur was heard in the tricuspid area, a snapping second sound in the pulmonic area. X-ray of his heart presented a uniform cardiac enlargement with an increase of the pulmonary conus and a rather diffuse increase of the vascular shadows throughout the lung fields. During our first study (Fig. 9) we found hypertension in the right ventricle of 92/0 mm. of mercury, associated with a peripheral systemic blood pressure of 110/67. The oxygen content of his right auricular blood was 18 volumes per cent and that of his

right ventricle 20 volumes per cent. At the time of this study we explained this difference of oxygen contents by the assumption that during certain phases of the cardiac cycle there was a small amount of arterialized blood flowing from left to right through



$$\text{Pulmonary blood flow} = \frac{190}{26-22} \times 0.1 = 4.8 \text{ L./min.}$$

$$\text{Systemic blood flow} = \frac{190}{24-18} \times 0.1 = 3.2 \text{ L./min.}$$

Arterial saturation at rest = 86%

Arterial saturation after exercise = 60%

Hemoglobin = 21 Gm.

Hematocrit = 74%

FIG. 9. Summarizing the relationships in D. F. Compare with Figure 7.

the ventricular septal defect. We were unable to pass the catheter into the pulmonary artery. The oxygen content of his femoral arterial blood was 24 volumes per cent, an oxygen saturation of 86 per cent; following our standard mild exercise, the oxygen saturation of the arterial blood dropped to 60 per cent. We repeated our right heart catheterization studies and were successful in passing the catheter into the left pulmonary artery as you can see from this x-ray. (Fig. 10.) During these studies we were able to obtain blood samples from the right auricle, ventricle and pulmonary artery. We found an oxygen content of 18

volumes per cent in the right auricle, 20 volumes per cent in the right ventricle, 22 volumes per cent in the pulmonary artery and 24 volumes per cent in the femoral artery. We must again assume an oxygen content of 26 volumes per cent for the blood returning from the lungs to the left heart. By subtracting the oxygen content of his pulmonary arterial blood from that assumed for the pulmonary vein blood we obtain a pulmonary arteriovenous oxygen difference of 4 volumes per cent which divided into the minute oxygen intake of 190 cc. gives us a pulmonary blood flow of 4.8 liters per minute. Similarly, the systemic blood flow is calculated by using the oxygen difference between the femoral arterial and right auricular bloods, 24 minus 18, a difference of 6 volumes per cent. When divided into the oxygen intake of 190 cc. per minute, this gives us a systemic blood flow of 3.2 liters per minute. Thus we are able to show that in this patient the pulmonary blood flow is greater than the systemic, indicating the presence of a collateral circulation from the aorta to the pulmonary artery, such as a patent ductus arteriosus.

DR. LOEB: I would just like to ask, Dr. Richards, if Dr. Humphreys made a better patent ductus with the subclavian artery than he has already, would the patient be further improved?

DR. RICHARDS: The boy is spitting up large quantities of blood.

DR. LOEB: You think that is the result of his ductus at the present time?

DR. BALDWIN: That is the result of the congestion in the lungs. Certainly by x-ray they show very dark and thick vascular shadows.

DR. LOEB: Another thing I would like to ask is whether or not you are justified in assuming that there are 26 volumes per cent of oxygen in the pulmonary vein in an individual who has as much back pressure in the lungs as this patient has had for a long time?

DR. RICHARDS: If it were less, that would make the pulmonary blood flow even larger.



FIG. 10. X-ray showing catheter in the left pulmonary artery of D. F.

DR. BALDWIN: The smallest the pulmonary blood flow can be, assuming that the blood coming back from the pulmonary vein is 100 per cent saturated, is 3.9 liters which is still above his systemic circulation.

DR. RICHARDS: The polycythemic response is still not entirely solved, is it? In general, it corresponds with the amount of arterial oxygen unsaturation, but here is a boy with 86 per cent arterial oxygen saturation, a very marked polycythemia and presumably a very large excess blood volume; yet patient G. G., whom Dr. Humphreys operated upon to be the same as this boy now, has lost his polycythemia (at least for the time being) and is no longer cyanotic.

DOCTOR: Do you know what G. G.'s saturation is with exercise?

DR. BALDWIN: He was ill when he came in and we thought it best not to exercise him.

DR. RICHARDS: There are, of course, many different types of congenital anomalies, some of which can be successfully explored by these technics, some not. We have presented two of the most common types today, one of the non-cyanotic and one of the cyanotic group, and have not gone further into the more complicated types. Do you want to add anything, Dr. Cournand?

DR. COURNAND: In our experience with

the tetrad of Fallot, which is not as wide as Dr. Bing's in Baltimore who has catheterized over 100 patients, it is not unusual to find another anomaly, often an interauricular defect. That is how Dr. Baldwin occasionally is able to get pulmonary vein blood, or through such anomalies as implantation of the right pulmonary vein in the right auricle.

I think that it is extremely important to map out all the malformations, if possible, because the problem insofar as the surgical service is concerned is certainly different if the tetrad of Fallot is complicated by still other abnormalities. In the causation of cyanosis perhaps the most important factor is the degree of over-riding or right-sided displacement of the aorta. I believe that by our methods we can detect the amount of over-riding of the aorta. It is quite striking that the tetrad of Fallot may be associated in some cases with normal or fairly normal oxygen saturation at rest; while in others there is a very marked oxygen unsaturation at rest which is directly related to the degree of over-riding.

There is another point which I would like to mention. Although the tetrad of Fallot is supposed to have atresia or marked stenosis of the pulmonary artery, it is almost the rule that catheterization of the pulmonary

artery can be carried out with success; Dr. Bing found out, after many trials, that it was possible to pass a catheter into the pulmonary artery in almost every patient. This means that there are very few patients with real atresia and most of these patients have pulmonary stenosis.

That is about all I have to say except that follow-up studies which have been carried out on patients after Blalock's operation, chiefly in Dr. Blalock's clinic, show that the pulmonary blood flow had markedly increased and that the arterial oxygen unsaturation had markedly decreased. But it takes some time for the oxygen saturation to reach its best levels; I think it takes as much as two, three or four months to reach 86, 87 or 90 per cent.

There is one more thing which is rather interesting. There is a very marked decrease in the oxygen consumption in most of the children with congenital heart disease that have been studied. In other words, they have a basal metabolism which is consistently reduced before operation. That is borne out by the appearance of the children. After the operation the oxygen consumption is very markedly increased; the basal metabolism becomes normal.

DR. ROSS GOLDEN: What is the impression as to the value of angiocardiology?

DR. RICHARDS: I am glad you brought that up. Some of the patients at Bellevue have had it and in some instances it has been of great value. They have been subjects with large dilatations of one vessel or another. It identifies them very well. Do you want to say anything further about that, Dr. Courmand?

DR. COURMAND: We really have no competent study of patients by angiocardiology.

DR. RICHARDS: We have had one patient with aneurysm of the superior vena cava due to direct communication with one of the pulmonary veins. That was shown quite well by angiocardiology as far as the superior vena cava was concerned. It did not show the cause of the aneurysmal dilatation. In a case of hemangioma of the lung

the arterial-venous communication was shown by angiocardiology. In this instance catheterization methods could only show the great increase in pulmonary blood flow. I would say that the two procedures are supplementary and, if used together, can give additional information in some instances.

DOCTOR: We have done a few angiocardiological studies and in one case a connection between the right and left ventricles was shown.

SUMMARY

DR. FREDERICK K. HEATH: Congenital heart disease includes a wide variety of anatomic defects, about one-half of which produce significant physiologic abnormalities. This half, representing about 1 per cent of all organic heart disease and about 2 per cent of that seen in children, recently has become the center of great physiologic and surgical interest. For advances in vascular surgery have made it possible to achieve dramatic and often life-saving results in this group of patients. Coincidentally, investigation by means of the intravenous catheter had progressed so far that precise diagnostic and postoperative follow-up information could be obtained. This was important since it soon became obvious that clinical appraisal based only on physical findings and statistics gave neither accurate diagnosis nor quantitative information regarding cardiac function. Important, too, is the use of radiographic techniques whereby the abnormality may be visualized.

The four cases presented serve to illustrate present day techniques and their limitations, how data obtained by catheterization techniques are interpreted, and representative results of surgical therapy. They also emphasize the frequent occurrence of multiple defects.

By means of cardiac catheterization with simultaneous measurement of the blood oxygen content and pressures in the various chambers it is possible by application of the Fick principle to calculate cardiac output, to define the systemic and pulmonary cir-

culatation in terms of volume flow per unit of time, and to estimate, when present, the *direction* of shunt flow. In connection with pressure measurements it is to be remembered that an increase in pressure may result from obstruction to flow, e.g., stenosis of the pulmonary artery, in which case the rate of flow will be decreased; or on the other hand, it may simply be due to an increased rate of flow *per se*. It is clear that information both as to pressure and rate of flow are important for interpretation.

Accurate anatomic and physiologic estimations are of invaluable aid in deciding whether or not operative interference should be helpful. Thus in simple patent ductus arteriosus an excellent result is to be expected. Of twenty-six uncomplicated cases of this condition operated upon by Dr. Humphreys only one death occurred postoperatively and only one proven recur-

rence was noted. When the patent ductus arteriosus is complicated by other defects, the outlook depends upon the nature of these complications. In this group the operative mortality and results are decidedly less favorable.

When indicated, i.e., cyanotic heart disease, the creation of an artificial ductus, as carried out by Dr. Blalock, may relieve cyanosis but it also increases the pulmonary blood flow and the work of the heart. Whether eventual cardiac hypertrophy and failure, pulmonary congestion and polycythemia may be postoperative sequelae is not yet clear. These findings were observed in one patient thought to have a tetrad of Fallot plus a patent ductus arteriosus from birth; yet in patients receiving an artificial ductus the disappearance of polycythemia has been encountered.

Clinico-pathologic Conference

Convulsions and Hepatic Disease^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, D. R., (B. H. History No. 141,029), a forty-four year old white married housewife, entered the Barnes Hospital on November 11, 1946, because of convulsions. Because the patient herself was never in any condition to supply information, the history had to be obtained from her husband. The family history was of interest only in that two weeks prior to admission the patient had been exposed for one week to an aunt with tuberculosis. The patient had apparently enjoyed excellent health most of her life. Twenty years before entry she had undergone an appendectomy and fifteen years before admission her uterus, Fallopian tubes, the left ovary and a "portion" of the right ovary were removed. Subsequent to the gynecologic operation she took "sheep glands" but no information was obtainable in regard to her menstrual periods.

One year before coming to the hospital the patient began to experience hot flashes and other signs of menopause. She consulted a physician who gave her injections of an unknown nature and pills identified as ben zestrol (octofollin); it was thought that she took twice the prescribed dose of the latter medication. She apparently drank large amounts of water, as much as five or six glasses during the night, and voided frequently. Approximately nine months before admission she had coated the walls of her kitchen with chlorox (sodium hypochlorite). The following day she developed anorexia, nausea and vomiting and these symptoms persisted for two weeks. Because

she became very nervous, a physician prescribed elixir of alurate. Three or four months before entry she used a hair bleach and again developed severe nausea and vomiting. It was reported that she smoked two packages of cigarettes daily, drank approximately 1 pint of whiskey daily and ate irregularly. Her husband stated that the patient had always bruised easily.

One day before entry the patient seemed unusually well and much less nervous than she had been previously. That evening, however, she became intoxicated and at 3 A.M. awoke with a severe headache. Three hours later she had the first of several attacks of generalized shaking movements lasting a few minutes. During each of these episodes she was described as becoming rather rigid; her legs were extended, her arms were flexed and she shook violently. Her eyes were said to have "rolled upward." Between convulsions she was unconscious and breathed "hard." Attempts on the part of her family to reach the family physician were without avail and eighteen hours after the onset of her headache the patient was brought to the Barnes Hospital.

At the time of entry physical examination revealed her temperature to be 40.4°C., pulse 136, respirations 36 and blood pressure 130/105. The patient was a well developed, obese woman who appeared to be the stated age. She was semicomatose and mumbled incoherently at times. During the course of examination she had repeated generalized clonic convulsions at fifteen-minute intervals. The skin was dry and many purpuric

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

spots were seen. The head appeared normal; no evidence of trauma was noted. The eyeballs were soft. The pupils were dilated but reacted well to light; examination of the fundi showed a few patchy white areas along the vessels but there were no hemorrhages seen and the discs appeared normal. One observer detected the odor of acetone on the patient's breath but another examiner did not agree. The neck was not stiff. Examination of the lungs revealed them to be clear to percussion and auscultation. Because of stertorous breathing, the heart sounds could not be heard well but the heart was normal in size and no murmurs were described. The liver was slightly enlarged but the spleen could not be felt and no other abdominal masses were palpable. Neurologic examination showed no signs of meningeal irritation. The extremities were held in extension; the tendon reflexes were hyperactive throughout, particularly on the left. Positive Babinski and Hoffmann signs were elicited on the left.

Laboratory findings were as follows: Blood count: red cells, 4,260,000; hemoglobin, 13.9 Gm.; white cells, 6,340; differential count: juvenile forms, 1 per cent; stab forms, 13 per cent; segmented forms, 64 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Urinalysis: (after intravenous glucose) specific gravity, 1.018; pH, 5.5; albumin, 2 plus; sugar, 3 plus; acetone, 3 plus; sediment, 3 red blood cells per high power field. Blood chemistry: sugar, 176 mg. per cent; carbon dioxide combining power, 54.5 volumes per cent; sulfadiazine, none found. Icterus index: 61. Spectroscopic examination of the plasma (on admission): oxyhemoglobin, positive; methemoglobin, questionable trace; hemoglobin, negative; porphyrin, negative; carboxyhemoglobin, negative. Spectroscopic examination of the urine (on admission): hemoglobin, negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood culture: negative. Electrocardiogram: left axis deviation and sinus tachycardia.

On admission to the hospital diabetic acidosis was suspected; no urine could be

obtained, even by catheterization, and the patient was given 1,000 cc. of 5 per cent glucose in saline intravenously and 1,000 cc. of 1/6 molar lactate and 25 units of regular insulin subcutaneously. A lumbar puncture was then performed. The initial pressure was 105 mm. in water. The fluid was clear and contained fifty red cells which were not crinkled and were thought to have been due to trauma incident to the procedure itself. The other studies were as follows: protein, 48 mg. per cent; sugar, 113 mg. per cent; chloride, 431 mg. per cent; colloidal gold curve, 0000000000; Wassermann test, negative. The patient was seen in consultation by a neurologist who recommended the administration of 100 cc. of 50 per cent sucrose intravenously and avertin per rectum to control the recurring convulsions.

A second specimen of urine was obtained; it was considerably darker in color than the first. The benzidine test was strongly positive but tests for urobilinogen and bilirubin were negative.

On the day following admission the patient was observed to have constant nystagmoid movements of the eyes. An ophthalmologic consultant was asked to see the patient; although examination was difficult, the discs appeared of good color and no new findings were noted in the optic fundi. It was thought that the white areas represented old choroiditis. The neurologic findings were those of decerebrate rigidity. Blood counts were within normal limits. Urinalysis revealed specific gravity of 1.050 with 4 plus albuminuria but the urine was free of sugar, acetone or porphyrin. Urobilinogen was present in a dilution of 1:50 and the benzidine test was strongly positive. The sediment revealed a few red blood cells. Repeated blood cultures were sterile. The icterus index was 100 and the prothrombin time was normal. Tenderness was elicited over the liver and faint jaundice became apparent.

Further laboratory studies were as follows: non-protein nitrogen, 28 mg. per cent; blood sugar, 56 mg. per cent; cephalin-cholesterol flocculation test, 3 plus; pro-

thrombin time, 92 per cent of normal; bleeding time, $11\frac{1}{2}$ minutes; clotting time, $5\frac{1}{2}$ minutes. Blood platelet count: 55,000. Bromsulfalein dye retention: 100 per cent in 30 minutes. Van den Bergh test: direct, 5.37 mg. per cent; indirect, 6.82 mg. per cent. The urine sediment showed many granular casts and bacilli; on culture, coliform organisms were reported.

On the third hospital day the patient's sensorium was much clearer and she was partially oriented; she was able to answer questions and to carry out simple commands. The physical findings were unchanged except for the presence of Trousseau's sign which was attributed to hyperventilation. The temperature fell to 38.5°C . and blood cultures continued to be sterile. Urinalysis revealed 4 plus albumin; the sediment showed numerous casts; the benzidine test was negative. The patient's urinary output gradually diminished and her non-protein nitrogen rose slightly to 33 mg. per cent. The serum protein was 4.8 Gm. per cent with 2.9 Gm. per cent albumin and 1.9 Gm. per cent globulin. The blood calcium was 7.3 mg. per cent and the blood phosphorus 3.5 mg. per cent. The icterus index had fallen to 41 units.

On the fourth hospital day examination of the lungs revealed signs suggestive of early pneumonia at the right base. The white blood count and differential remained at normal levels. Penicillin therapy was instituted. Later that night the patient became cyanotic and oxygen was given by a nasal catheter. Because of increased mucus in the tracheobronchial tree, endotracheal suction was employed. The patient had several seizures during which she held her breath. She became extremely opisthotonic and held her hands in a tetanic position. Her neck was slightly rigid. Tetany was relieved by administration of calcium gluconate intravenously, but the patient failed rapidly and died early in the morning on November 15, 1946, her fifth hospital day.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: We are at a definite disadvantage in attempting to reach

a diagnosis in this case since the patient was too ill to supply her own history and the historical information obtained from her husband was not as complete as would be desired. I think we may proceed, however, by attempting first to define the anatomic lesions and second to identify their cause. Now the first event which apparently marked the onset of the final illness was a severe headache followed by convulsions. Dr. Levy, would you like to suggest a possible central nervous system lesion?

DR. IRWIN LEVY: I think it is entirely possible that no specific central nervous system lesions will be found.

DR. ALEXANDER: Do the spinal findings rule out meningeal involvement?

DR. LEVY: Yes, I think they enable us to do so. Furthermore, the fact that the spinal fluid pressure was normal seems to me to afford strong evidence that there was no real cerebral edema. In view of the finding of purpura the possibility of hemorrhagic encephalopathy must be raised. Against such a possibility, however, is the fact that the patient improved for a day or two prior to her death whereas patients with hemorrhagic encephalopathy usually have a progressively fatal course.

DR. ALEXANDER: Am I correct then in saying that if there is a central nervous system lesion, it will lie in the cerebral substance itself rather than in the meninges?

DR. LEVY: I would agree with that statement.

DR. W. BARRY WOOD, JR.: Dr. Levy, why did this patient have convulsions?

DR. LEVY: I am unable to answer your question. During her hospital stay she had definite tetany and it is conceivable that the so-called convulsive episodes were manifestations of decerebrate rigidity during tetany. Prior to the onset of these convulsions she had been intoxicated, and the possibility of alcoholic intoxication being a contributing factor must also be mentioned.

DR. ALEXANDER: Dr. Wade, do you believe that the patient had severe structural liver damage?

DR. LEO J. WADE: Certainly the 100 per cent retention of bromsulfalein at thirty

minutes indicates rather profound liver impairment and I believe that the clinical history suggests the diagnosis of cirrhosis of the liver. It is conceivable that on two occasions hepatic insult resulted from exposure to noxious agents. I am referring to the chlorox and to the hair dye. After she was in contact with each of these substances she developed symptoms which suggested intoxication.

DR. ALEXANDER: Would you consider that the patient had acute hepatitis without cirrhosis?

DR. WADE: I think it is more likely that acute hepatitis may have been superimposed on cirrhosis; I doubt that the brief exposures to the two toxic agents mentioned were sufficient to have caused the degree of liver damage indicated by the abnormal liver function tests had not the organ already been seriously compromised.

DR. ALEXANDER: Do you believe this patient had a renal lesion, Dr. Schroeder?

DR. HENRY A. SCHROEDER: No, I think that dehydration was responsible for the urinary findings and I doubt that she had significant renal disease.

DR. ALEXANDER: In view of the fact that the albuminuria varied between 2 and 4 plus, that red cells and casts were found in the sediment and remembering that the non-protein nitrogen rose, would you like to entertain the possibility that the patient had acute nephritis?

DR. SCHROEDER: The non-protein nitrogen was really not elevated to a marked degree and I would therefore be inclined to attribute the rise to prerenal azotemia.

DR. ALEXANDER: I presume you would likewise explain the albuminuria and hematuria on that same basis?

DR. SCHROEDER: Yes, I would.

DR. ALEXANDER: Dr. MacBryde, what is your view on this point?

DR. CYRIL M. MACBRYDE: I agree with Dr. Schroeder. I do not believe that there will be serious structural changes in the kidneys.

DR. WADE: Are the renal findings not compatible with a diagnosis of arteriolar nephrosclerosis? The patient had an elevated

diastolic pressure and the urinary findings are consistent with that diagnosis.

DR. ALEXANDER: The ophthalmoscopic findings were not particularly significant in the opinion of the house staff nor in the opinion of the ophthalmologic consultant. However, your suggestion is quite interesting.

DR. WADE: If this patient did have arteriolar nephrosclerosis, it is conceivable that the nervous system manifestations represented hypertensive encephalopathy.

DR. WILLIAM H. OLMSTED: I should like to suggest that hematuria was just another manifestation of the underlying process which led to purpura. In view of the fact that the patient was an alcoholic who did not enjoy a satisfactory diet the abnormal bleeding may have been based on a vitamin deficiency.

DR. ALEXANDER: Would a vitamin C or K deficiency lead to such a low platelet count? You will recall that the patient had only 65,000 platelets and the normal value in this hospital is between 400,000 and 800,000. I believe the low platelet count suggests profound damage to the bone marrow itself. Dr. Futcher, would you comment on the abnormal blood chemical findings? This patient had a low total serum protein and low calcium but the albumin-globulin ratio was normal.

DR. PALMER H. FUTCHER: I cannot explain the hypocalcemia. I do not believe that the protein was low enough to have depressed the calcium to the degree reported here.

DR. ALEXANDER: Let us now consider further the problem of hepatic damage. The patient had used a hair bleach, barbiturates and large amounts of alcohol. I am told that hair bleach is usually hydrogen peroxide; at times ammonia is added. She had likewise taken large quantities of estrogenic substances and on one occasion was exposed to chlorox. Dr. Shaffer, would you comment on the toxicity of chlorox.

DR. PHILLIP A. SHAFFER: Chlorox is quite a toxic substance but the brief exposure to chlorox which this patient underwent while washing her kitchen walls does not seem to

me to merit serious consideration as a cause of her final illness.

DR. ALEXANDER: May barbiturates produce convulsions; Dr. Levy?

DR. LEVY: In cases of severe barbiturate poisoning convulsions do occur, but rarely. As a matter of fact, as you know, barbiturates are used ordinarily to control convulsions.

DR. ALEXANDER: Would you care to comment, Dr. Graham?

DR. HELEN GRAHAM: My information regarding the composition of hair bleach is essentially the same as yours, Dr. Alexander. I agree with Dr. Levy's statement on barbiturates and convulsions.

DR. ALEXANDER: May barbiturates effect the liver?

DR. GRAHAM: Since alurate is a barbiturate with long action, it is probably not destroyed by the liver. It is said, however, that damaged livers may be further injured by large doses of barbiturates. The amount of alurate taken by this patient was uncertain, as I understand it, and therefore we cannot draw specific conclusions here.

DR. ALEXANDER: Would you comment on the effect of alcohol on the kidneys, Dr. Schroeder?

DR. SCHROEDER: It is said that for each martini one drinks, one glomerulus is lost. I know of no experimental evidence, however, which indicates that alcohol damages the kidney.

DR. ALEXANDER: Let us now consider the effect of the estrogens that this patient received. Dr. Allen, would you comment on benzestrol?

DR. WILLARD M. ALLEN: Benzestrol is a synthetic compound closely related to stilbestrol; it is 2, 4-di(p-hydrophenyl)-3-ethyl hexane. The synthetic estrogens in use today are by and large non-toxic. I know of only one case report of jaundice that was due to stilbestrol. Perhaps Dr. MacBryde would comment further on this point.

DR. MACBRYDE: In the experimental animal extremely large doses of any estrogen may cause toxic effects, among which are numbered hepatic damage and damage to

the bone marrow. I believe that there have been several cases in which evidence favored the fact that the natural estrogens have been responsible for some hepatic damage. I do not believe that the synthetic estrogens are any more toxic than naturally occurring estrogens. Dr. Castrodale, Dr. Helwig, Miss Bierbaum and I studied this particular problem in dogs, using comparable amounts of estradiol and stilbestrol.¹ With both types of estrogen, there were profound effects on the bone marrow with leukopenia, severe anemia, thrombocytopenia, hemorrhages, etc. We also found evidence of fatty infiltration in the liver if either estrogen was given for a long enough time.

DR. ALEXANDER: Do you believe that the toxic effect of estrogen on the bone marrow may have led to hemolysis of red cells?

DR. MACBRYDE: I know of no evidence in that regard.

DR. ALEXANDER: It seems possible that most of the alcohol and the estrogens affected the liver adversely and the changes in the blood may perhaps have been due to estrogens. Conceivably the convulsions may have been due to alcoholic intoxication. The hemoglobinuria is unexplained.

DR. FUTCHER: Is it possible that this patient had Weil's disease?

DR. WOOD: That is a very good suggestion I believe. She had fever, evidence of liver damage, rising non-protein nitrogen, urinary abnormalities and petechiae. Weil's disease is due to an organism which is called *Leptospira icterohemorrhagiae* and this patient was icteric and had hemorrhagic lesions.

DR. FUTCHER: In general, leukocytosis is seen in Weil's disease and this patient had no elevation of the white count which militates against that diagnosis.

DR. ALEXANDER: In summary, this patient probably had liver disease, possibly cirrhosis with superimposed hepatitis due to exposure to estrogenic substances. If she had

¹ CASTRODALE D., BIERBAUM, O., HELWIG, E. B. and MACBRYDE, C. M. Comparative studies of the effects of estradiol and stilbestrol on the blood, liver, and bone marrow. *Endocrinology*, 29: 363, 1941.

cirrhosis, it is probable that it arose as a result of long-standing alcoholism. The general consensus of opinion is that she did not have serious renal disease but that the abnormal urinary findings represented changes due to prerenal azotemia. The possibility of vitamin deficiency has been raised and Weil's disease has been suggested. It is thought that the patient probably did not have a central nervous system lesion *per se*.

Clinical Diagnosis: Cirrhosis of the liver; ?toxic hepatitis due to estrogens; ?avitaminosis C or K; ? Weil's disease.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: At the time of autopsy external examination revealed an obese white female with definite icterus of the sclerae and questionable icterus of the skin. Over the entire skin surface numerous purple to brown small pigmented areas measuring 1 to 3 mm. in diameter were seen. These were neither elevated nor ulcerated. Inspection of the viscera showed numerous petechiae in the serous membranes of the body cavities and there were also hemorrhages in the mucosa of the entire gastrointestinal tract and in the mucosa of the bladder; very small hemorrhages were seen in the meninges. On gross examination the brain showed no visible pathologic changes and multiple sections after fixation revealed no evidence of hemorrhage or encephalomalacia. The most striking anatomic change was in the liver which was enlarged, weighing 2,650 Gm. The capsule was smooth and the substance was diffuse yellow in color. The lobular markings were indistinct. There was no accentuation of the periportal fibrous tissues. After fixation the central portions of the lobules acquired a faint green stain. The pancreas was normal in size; in its substance there were a few small areas of fat necrosis. The kidneys appeared normal. The lungs were heavy, weighing 890 Gm. There was total atelectasis of the right lower lobe and partial atelectasis involving the lower portions of both upper lobes. There were no gross

changes which could be interpreted as consolidation. The spleen was slightly enlarged and weighed 180 Gm.

DR. ROBERT A. MOORE: As Dr. Johnson has told you, the gross anatomic changes in general were not very striking. There was a fatty liver, a few foci of fat necrosis about the pancreas and petechiae and ecchymoses in various parts of the body. Before discussing the diagnostic possibilities further let us examine the microscopic sections. Figure 1 is a section of the liver showing the character of the pathologic change. There is a moderate to severe degree of fatty infiltration in the liver. The liver cells are distended by large vacuoles containing fat but there is no significant increase in the amount of connective tissue. The pathologic picture is not that of so-called fatty cirrhosis but represents rather fat infiltration or fatty metamorphosis. That the liver cells were still capable of some function is evidenced by the fact that a glycogen stain revealed the presence of glycogen in the cytoplasm of many cells. Conceivably the glycogen was deposited after the intravenous infusion of glucose. Figure 2 is from the pancreas. It shows an area of fat necrosis. The fat cells are no longer distinctly visible for the fat has been converted into granular, amorphous material without giving rise to much cellular reaction. The pancreatic lesions occurred toward the end of the patient's life and probably do not represent any change of clinical significance although they may aid us in arriving at our final evaluation. Figure 3 is from the heart and shows two types of change from the normal: First, there is interstitial edema which is evidenced by the separation of the muscle fibers and secondly, there is slight cellular infiltration. In Figure 4 another section of the heart muscle is seen showing the same changes just outlined plus some degenerative changes in the fibers. In Figure 5 these changes are seen under higher magnification. Most of the cellular infiltration is due to an increase in the myocytes of Anitschkow, a change which arises as a result of irritation in the myocardium. It is generally believed that

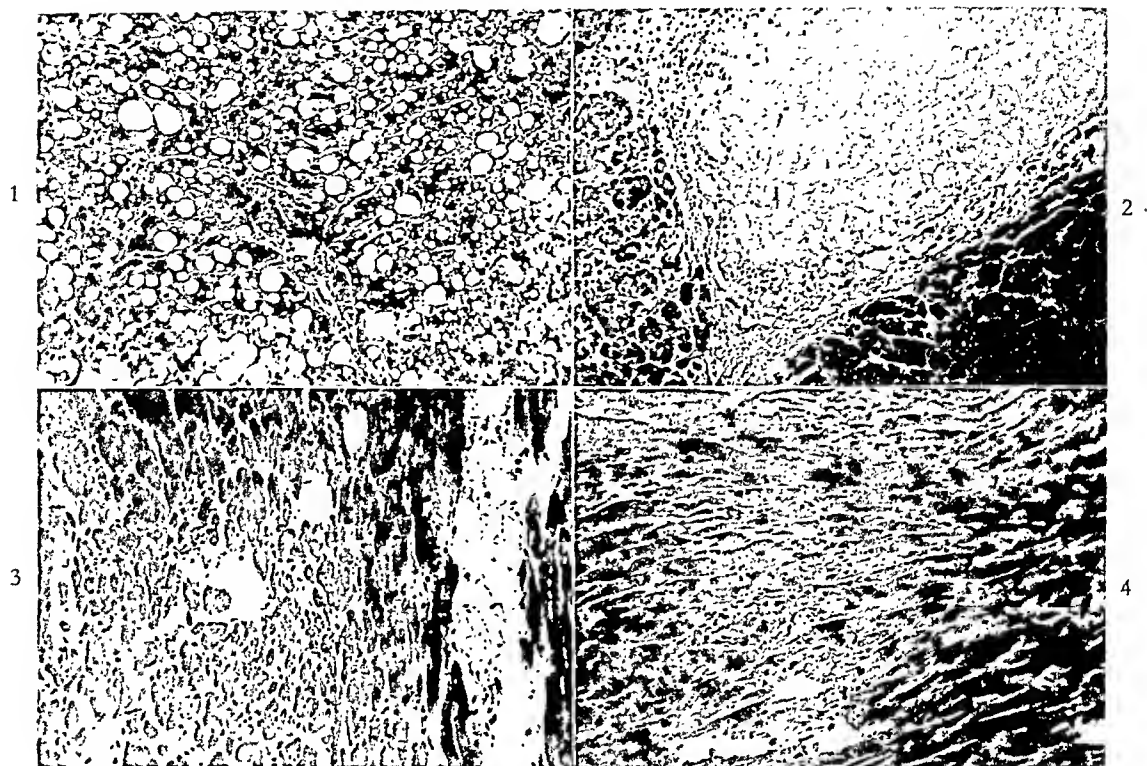


FIG. 1. Section of the liver showing the degree of fatty infiltration. Note that the amount of connective tissue is not increased over that seen normally.

FIG. 2. Section of the pancreas in an area of fat necrosis.

FIG. 3. Section of the myocardium showing interstitial edema and slight cellular infiltration.

FIG. 4. Another section of the myocardium showing the same changes seen in Figure 3.

the Anitschkow myocytes develop into Aschoff cells. In other words, almost any noxious stimulus may bring about activation of the myocyte of Anitschkow while in acute rheumatic fever the causative agent, whatever it may be, causes further change in the cells to the point when they take on the characteristics which we ascribe to Aschoff cells. In Figure 6 a section of skeletal muscle is seen. We examined a number of sections of the skeletal muscle and all showed the same change. The lesions were most advanced in the diaphragm and consisted of degeneration of the muscle fibers, proliferation or accumulation of sarcolemmal cells and slight infiltration of mononuclear cells. In other words, there is degeneration and slight inflammatory reaction in the striated muscles, both skeletal and cardiac. Figure 7 shows a section of the adrenal gland; one sees a zonal type of necrosis in the center of the cortex. Finally a section of the lung (Fig. 8) shows the

changes of terminal bronchopneumonia. The bronchi are filled with an exudate consisting of polymorphonuclear leukocytes and in some areas the alveoli are filled with a similar exudate.

In attempting to correlate the changes it will be well to list the pathologic changes which may be related to the primary disease: First, there is moderately advanced fatty metamorphosis of the liver; second, degenerative changes with some proliferation which involve the heart muscle and the skeletal muscle; third, in the pancreas there is focal fat necrosis; fourth, the bone marrow is generally hypoplastic, all the elements apparently being equally depressed and fifth, in the adrenal, areas of cortical degeneration were present. The negative observations may be of significance. There were no changes either grossly or microscopically in the central nervous system and the kidneys were normal grossly and microscopically.

Certainly the changes in the liver may be

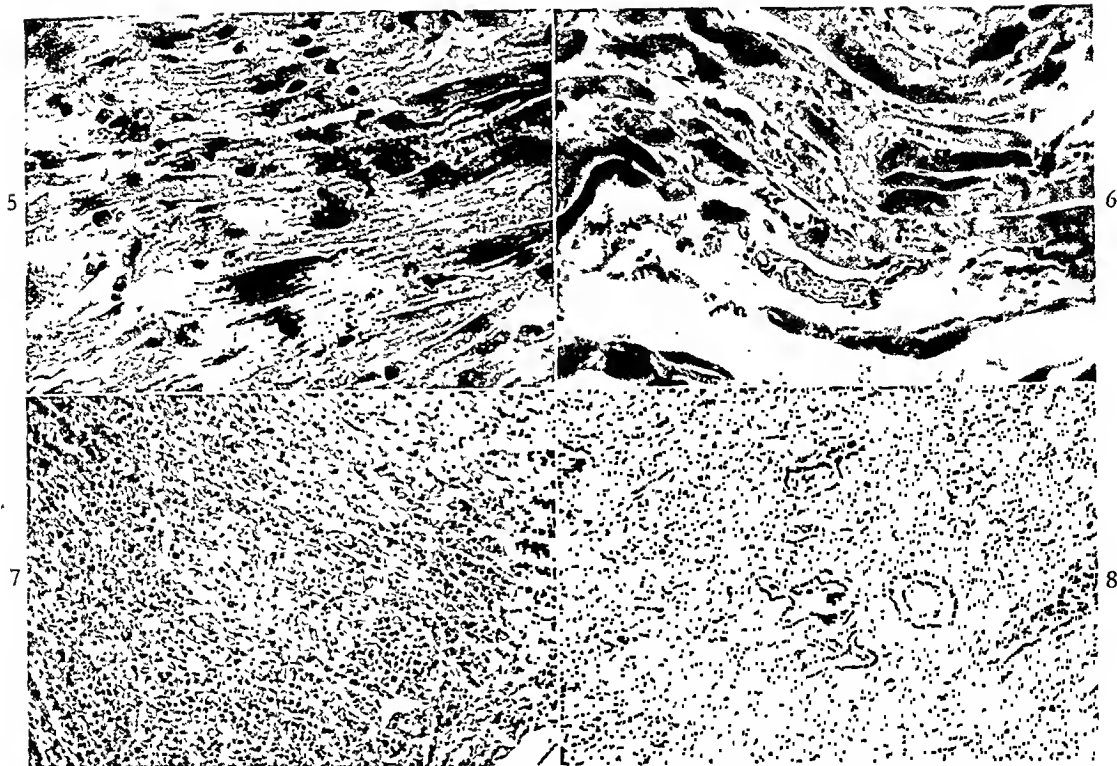


FIG. 5. Section of the myocardium seen with higher magnification. Note the increase in the Anitschkow myocytes.

FIG. 6. A section of skeletal muscle showing degenerative and proliferative changes.

FIG. 7. Section of the adrenal cortex showing the zonal type of necrosis.

FIG. 8. Section of the lung through an area of bronchopneumonia.

attributed to the chronic alcoholism for the lesion is well recognized pathologically.^{2,3} It has been recorded several times in patients who developed fatty metamorphosis of the liver in association with chronic alcoholism and who came into the hospital with convulsions; some of these patients have died soon after admission and at autopsy the only significant pathologic change has been the fatty metamorphosis in the liver. Likewise pancreatic changes, such as those described herein, have been observed not infrequently in chronic alcoholics. Changes in the striated muscle are similar to those which have been described by Follis⁴ as vitamin B deficiency or they may be produced by combining thiamine and potassium deficiency.

² LE COUNT, E. R. and SINGER, H. A. Fat replacement of the glycogen in the liver as a cause of death. *Arch. Path.*, 1: 84, 1926.

³ GRAHAM, R. L. Sudden death in young adults in association with fatty liver. *Bull. Johns Hopkins Hosp.*, 74: 16, 1944.

⁴ FOLLIS, R. H., JR. Myocardial necroses in rats on a low-potassium diet prevented by thiamine deficiency. *Bull. Johns Hopkins Hosp.*, 71: 235, 1942.

May the changes in the bone marrow and in the adrenal have resulted from the long continued use of estrogenic substance? The bone marrow changes particularly may possibly have been due to the estrogens for the changes were those of general hypoplasia rather than of inanition.

The clinical correlation in this case is not too satisfactory. The encephalopathic symptoms may have been due to hepatic damage or possibly to thiamine deficiency. We are unable to explain the tetany and the cause of the petechial hemorrhages is still obscure. I assume from the clinical discussion that hypoprothrombinemia was excluded on the basis of the normal prothrombin time. The changes in the megakaryocytes in the bone marrow were not impressive, certainly not to the point at which one would be willing to attribute the hemorrhage to thrombocytopenia. That the hemorrhage could have been due to low fibrinogen seems unlikely. Although the blood proteins were lower than normal, it does not seem likely

that they were low enough to allow the fibrinogen to become significantly depressed. It is the last element whose level falls and it is the rarest cause of hemorrhage. Vitamin C deficiency must certainly be considered. I do not think that either the hair bleach or chlorox should be considered as possible causative agents because of the remote exposure, but I do acknowledge Dr. Wade's point, namely, that a very fatty liver may have been much more susceptible than a normal one, even to brief exposures to these toxic agents. I do not think the changes are related to barbiturate. I believe we can rule out Weil's disease since the pathologic changes are not consistent with the diagnosis and in suitably stained sections no organisms could be demonstrated.

In summary we are left with the possibility that either alcoholism or estrogen toxicity were causative agents and I do not know how one could distinguish between them. Certainly the entire clinical picture with the exception of bone marrow changes may be explained on the basis of chronic alcoholism and the bone marrow changes may have resulted from large amounts of estrogens. Personally I believe the alcoholism was more significant than was the estrogen therapy. It is of interest that patients dying of fatty metamorphosis of the

liver do so during the winter. The syndrome is not seen in the summer.

DR. WOOD: Were the myocardial changes those of beri-beri?

DR. MOORE: Conceivably.

DR. WADE: Do you believe that the liver changes would have gone on to cirrhosis?

DR. MOORE: Yes, I do. Long-continued fat infiltration in the liver will result in fibrous proliferation.

Final Anatomic Diagnosis: Fatty metamorphosis of the liver, advanced (history of chronic alcoholism); petechiae in skin, serous membranes, mucus of stomach, small and large intestines, endocardium, mucosa of trachea and bronchi; focal hemorrhages in mucosa of bladder and in subarachnoid space, slight; atelectasis of entire lower lobe of right lung and dependent portions of all lobes; bronchopneumonia; fat necrosis in body and tail of pancreas; focal necroses in the cortex of the adrenal glands; degeneration of skeletal muscle with proliferation of sarcolemima; focal degeneration of myocardium with proliferation of myocytes, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Gout in a Negro Family*

ABRAHAM COHEN, M.D.

Philadelphia, Pennsylvania

THERE is little if anything in medical literature on the incidence of gout among the Negro people. This report concerns two of three Negro brothers who have gout. They exhibit the classic manifestations of tophaceous gout, as indicated in Figures 1 to 9.

It has always been thought that gout was a disease of the gourmand and the wealthy. The mode of life of these patients would hardly be considered that of gourmands and they were certainly not of the wealthy class.

Gout has been reported in these Negro patients on another occasion.¹ However, since the last report another brother has developed the disease. Opportunity is taken here to report on the progress of the disease in these patients.

CASE REPORTS

CASE I. J. A., a Negro male, born in South Carolina in 1914, 5 feet 9 inches tall, weighed 128 pounds. He had the ordinary diseases of childhood. The family history was irrelevant except that a younger brother has gout.

The onset of the present illness dates back to when he was twelve years of age. At this age he would awaken during the night with stiffness and swelling in the right knee. This lasted for a week, was not accompanied by pain and did not confine him to bed. He made a complete recovery. A year later he was awakened one night by severe pain in the right knee and found that the joint was swollen. The pain and swelling lasted for ten days, were confined to the knee and did not keep the patient in bed. He again made a complete recovery. At this time the patient was residing in the country in South Carolina. The family was poor and could afford only an ordinary diet. The patient ate sparingly of proteins and was not a drinker of alcohol.

About two years later, while at work one morning, he noticed swelling in the right great toe and left ankle. Soon there was redness, heat and severe pain. A few days later the right knee became involved and the patient was forced to bed for the first time. Here he remained, unat-



FIG. 1. Gout involving all toes in Negro.

tended by a physician for two weeks. A good recovery was made without residual signs or symptoms and no further difficulty was experienced until six years later, at the age of twenty-two, when at work pain and swelling developed suddenly in the right metacarpophalangeal joint. This attack was very painful and lasted for one week. The following week the right elbow became similarly involved. This was followed by involvement of the left great toe, right ankle and right knee. All joints were red, hot, swollen and extremely painful. Three weeks were spent in the hospital where treatment was given for arthritis.

There were ten more visits to the hospital. Fever therapy, baking and massage, as well as the other forms of therapy ordinarily prescribed for arthritis were given trial. The longest stay in the hospital was nineteen days, the shortest seven days.

* From the Arthritis Clinic of the Philadelphia General Hospital.



FIG. 2. X-ray of right foot in Figure 1.



FIG. 3. X-ray of left foot in Figure 1.



FIG. 4. Gout of hands in Negro.

The ears showed tophi. (Fig. 9.) Heart, lungs and abdomen were normal. The extremities showed large tophi involving both olecranon bursae, wrists, fingers, knees and toes. It was necessary to amputate one toe since its increase in size made it extremely difficult for the patient to walk. The blood uric acid varied from 11 to 5 mg. per cent.

His diet consists of whatever he can get and he takes colchicin whenever he can get it. Due to the shortage of colchicin during the war period and even at the present time, he seldom takes it unless we can find it for him. In the

interim we have watched him go from bad to worse until on one occasion we found it necessary to amputate a toe so that walking could be facilitated.

Of all the cases of gout seen by the author this has been the most fulminating.

CASE II. P. A., a Negro male, born in South Carolina in 1924, had the ordinary diseases of childhood. One brother has tophaceous gout. At the age of twelve, during the night, he was suddenly awakened with severe pain in the left



FIG. 5. X-ray of right hand in Figure 4.



FIG. 6. Gout of hands in Negro.

heel. In the morning there was swelling accompanied by pain along Achilles tendon. The attack was confined to the heel and lasted about two weeks. He made a good recovery without residual signs or symptoms.

Two years later, at the age of fourteen, he was again awakened in the night with pain, swelling and extreme tenderness in the left great toe. This time the attack lasted a week. No other joints were involved.

The third attack came at the age of sixteen; the right great toe and left ankle were involved. The patient was confined to bed for ten days.

There was swelling, redness and severe pain particularly at night. At the end of ten days recovery was complete except for the residual swelling. He has averaged two attacks yearly ever since.

Examination reveals a negro boy, twenty-two years of age, weighing 118 pounds, 5 feet, 3 inches in height. His blood uric acid (serum) is 6.1 mg. per cent. X-ray examination of the left great toe shows a punched-out area at the left first metatarsophalangeal joint.

Since the age of twelve this patient gets about four attacks yearly. He has tophaceous gout.

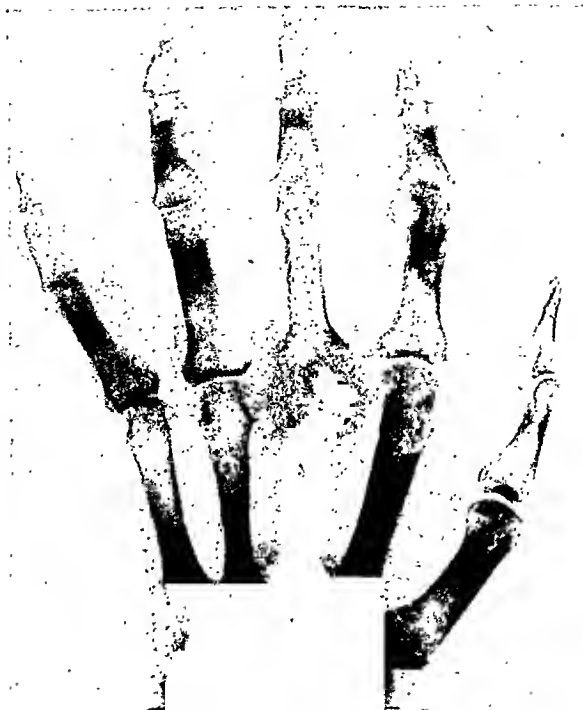


FIG. 7. X-ray of left hand in Figure 4.



FIG. 8. Gout of olecranon bursae in Negro.

The blood uric acid ranges from 7 to 5.5 mg. per cent.

During the last two years another brother, older than J. A., has developed pains in his joints described by J. A. as typical attacks such as he himself has. There are tophi in the ear cartilages. He refuses to visit the hospital nor does he wish to be seen by a physician.

Table 1 represents the genealogy for three generations as obtained from the family bible.

In 1938 the author² suggested a method for prevention of attacks of gout. It is of interest to note that our patients with presumptive gout who adhere to the regimen as described consider themselves to all in-

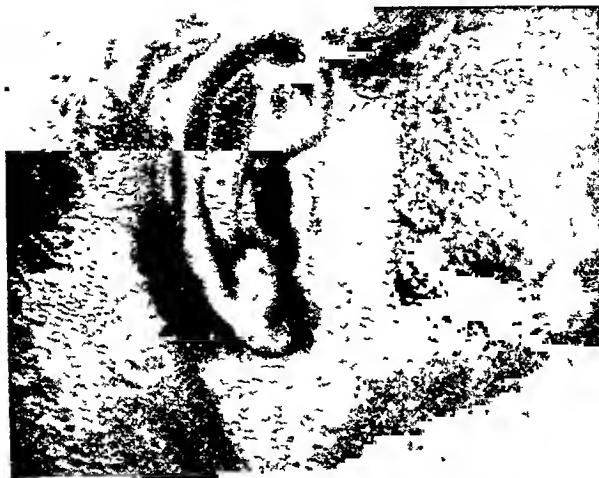
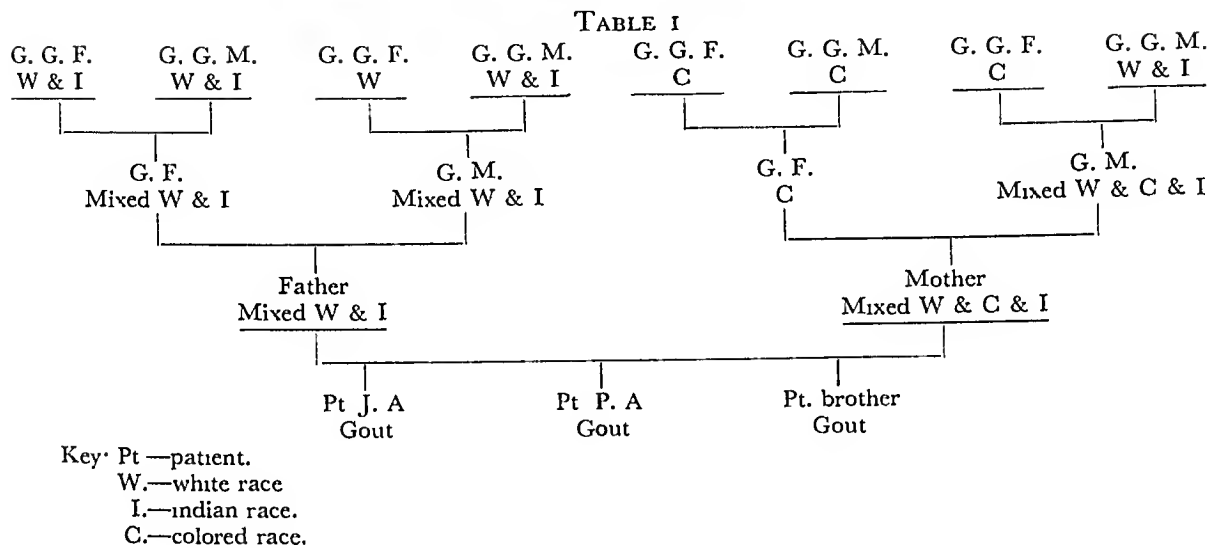


FIG. 9. Tophus in ear cartilage of Negro.



tents and purposes "cured." With proper regulation of the diet, abstinence from alcoholic beverages, proper administration of colchicin (and barring surgery, infection and accidents), one need never have a recurrent attack of acute gout. On the other hand while our tophaceous cases rarely get attacks, the progress of this disease goes on

unabated. Such has been the experience of the patient in Case 1 and of all those with tophaceous gout under our care.

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Long-standing Case of Widespread Tuberculosis and Acute Colon Bacillus Infection Treated by Streptomycin

WM. EGBERT ROBERTSON, M.D.

Philadelphia, Pennsylvania

ALTHOUGH the Actinomyces group has been studied by Waksman since 1919,¹ the production of streptomycin from Actinomyces griseus, the most recent to be studied, has until recently been very limited. In April, 1944, a small amount was placed in the hands of Doctors Hinshaw and Feldman of the Mayo group by Dr. S. A. Waksman. These investigators stated that "This amount was adequate to treat only four tuberculous guinea pigs for a limited period, but the results were sufficiently impressive to cause us to visit Dr. Waksman's laboratory immediately, in order to discuss these findings and to plan for future studies on an adequate scale. The amount of material required for such experiments was beyond the productive capacity of Dr. Waksman's experimental laboratory, but with his help it was possible to enlist the aid of Merck & Company who soon supplied streptomycin for earlier experimental problems.² Thus it has become possible for the Mayo group to treat "more than one hundred patients who had various infectious diseases" and to initiate a valuable and highly encouraging experimental study of tuberculous guinea pigs. This latter study by Feldman, Hinshaw and Mann³ furnishes a greater degree of encouragement than does the clinical study of streptomycin in human tuberculosis by Hinshaw and Feldman.⁴ In the experimental work forty-nine guinea pigs were used, twenty-four untreated controls and twenty-five treated by 1,500 units of streptomycin given subcutaneously every six hours, beginning on the forty-ninth day after inoculation with a human

strain of Mycobacterium tuberculosis and continuing for 166 days. Seventy per cent of the controls died before the study was completed and all but two of the treated guinea pigs survived. Most remarkable was the fact that thirteen of the treated animals recovered and no trace of the infection was found except for a calcified tubercle in the lung of one animal. In eleven of the remainder microscopic tubercles were found in the spleen, all retrogressing, seven of them being calcified, three fibrotic and one an epithelioid lesion.

Much less favorable is the impression gained by the study of thirty-four cases of tuberculosis in humans by Hinshaw, Feldman and colleagues previously referred to. They insist upon the time factor as a very necessary condition in judging the results, also the importance of not neglecting the use of rest, pneumothorax and any other measures previously found of value in the management of human tuberculosis. In the sixteen pulmonary cases the results were not spectacular, but streptomycin was limited in amount and dosage was not definitely established at that time. Clinical improvement did not run parallel with roentgenographic improvement but in two patients with miliary tuberculosis, one of whom had renal tuberculosis, improvement was "unmistakable and striking." This latter patient and four others with genitourinary tuberculosis, all having but one kidney, gave more satisfactory results. In four of these patients the Mycobacterium tuberculosis disappeared from the urine in two to four weeks, remained absent during the period

of one to four months during which they were under observation and the organism was not recovered, either by culture or by guinea pig inoculation. In the fifth patient, the one with miliary tuberculosis, although roentgenologic examination of the lungs showed definite improvement, the organism persisted in the urine. Four subjects with tuberculous empyema treated by streptomycin introduced into the pleura were not benefited and the medicament proved irritating. Six patients had tuberculous skin lesions, three with "draining sinuses due to suppurative tuberculous lymphadenitis." These showed "prompt and striking response" to streptomycin. Too brief a period had elapsed to pass a final opinion; this was also true of a case of tuberculous laryngitis.

The authors point out that a larger series treated over a sufficiently long time and with sufficient dosage, which remains to be determined, may not sustain the relatively favorable impression which may be deduced from their report. They urge strongly against optimism at this time, just as did Dr. Hobart Reimann and co-authors⁵ in their five cases of typhoid fever treated by streptomycin. The author has recently seen a patient with typhoid fever who was given two million units daily intramuscularly and one million units by mouth. This patient died of hemorrhage of the bowel and perforation in the third week of the disease after five days of streptomycin.

In both of the granulomatous diseases, syphilis and tubercuosis, some years must elapse before final judgment can be passed as to the therapeutic value of penicillin in syphilis and streptomycin in tuberculosis although reports thus far published suggest at least a measure of encouragement, even more striking in syphilis treated with penicillin.

Much remains to be learned as to the efficacy of streptomycin, but its value has been definitely established in meningitis due to *H. Influenzae*, Friedländer bacillus infection (which also responds well to some of the sulphones given by vein), tularemia and in infections due to gram-negative

organisms involving the genitourinary tract and peritoneum. Thus far, it is of questionable value in undulant fever and typhoid fever. In this latter streptomycin is given also by mouth because it diffuses only slightly out of the bowel, most of it being recoverable in the stool⁶ and it causes fairly prompt disappearance of the typhoid bacilli from the stool, but they return if, for any reason streptomycin is stopped in the course of the disease. In pulmonary tuberculosis with tubercle bacilli present in the sputum, even though clinical improvement occurs, the organism has not disappeared from the sputum in the cases reported thus far. If streptomycin were really bactericidal *in vivo*, this would not be the case in such infections. In treating more chronic infections, if for any reason the administration of streptomycin is stopped, to be resumed at a later period, definite sensitization phenomena may occur, mentioned also by Hinshaw and Feldman.

In the case of widely disseminated tuberculosis the patient developed manifestations of a histamine-like reaction and hematuria soon after the remedy was originally injected, with chilliness, marked depression, lowering of blood pressure, anorexia, general muscular soreness and a rapid pulse. The hematuria did not cease until a weak silver nitrate solution was instilled into the bladder. Streptomycin was temporarily stopped and when it was resumed he developed a fever up to 100°F., depression, a marked drop in blood pressure to less than 90 systolic, a pulse rate of 120 to 130, chilliness and hematuria, although the unit dose was much smaller than in the initial period. In the beginning too, he developed vestibular phenomena but no deafness. In both instances hydrochloride was used, so that the manifestations were probably due to the remedy itself and not to any impurities.

Streptomycin has been given directly into the vein and into the pleura and subdural space.⁷ Most frequent and satisfactory is its administration by the subcutaneous or intramuscular route. It is only slightly irritating locally but of short duration, diffuses

rapidly and can be recovered from blood, urine, bile, ascitic fluid, pleural fluid, amniotic fluid, peritoneal cavity, aqueous and vitreous humors and small amounts in spinal fluid. The dose, avenue of administration and time are all factors in determining the rate of absorption and excretion. It is very soluble, one million units (1 Gm.) being taken up readily by 5 cc. or less of distilled water or physiologic salt solution, but the amount of diluent depends on the dose to be given every three or four hours during the twenty-four hours. It has also been administered by nebulization and has not been found to be irritating but recovery is then negligible in blood and urine.

Reactions undoubtedly occur, proportionate to the dose, and are even more marked with smaller doses when the drug is re-administered after a lapse in treatment. Now that streptomycin has been crystallized and hydrochloride produced, it would seem to indicate that the reaction is inherent and not due to impurities. Pyrogens in the diluting fluid must be considered but careful technic will minimize or prevent these. Then too, these are more apt to occur when intravenous injections are given, but marked systemic disturbances and mild febrile reactions are not infrequent with streptomycin when subcutaneous or intramuscular routes are employed.

CASE REPORT

A male, age forty-one, a practicing physician, was seen first in 1927 when a sophomore medical student. He had had minimal pulmonary tuberculosis and bilateral pleurisy, 35 ounces of clear serum being removed from left pleura, dry tap on right. He had been given a hypodermic of quinine and urea in the right arm and when the author first saw him he had partial paralysis with wrist drop and atrophy. Immediate operation was advised which was done by Dr. Wayne Babcock with good recovery and a useful hand. Underweight, but without definite evidence of pulmonary involvement, in 1928 he spent two months at Trudeau Sanitarium. Soon thereafter he developed an epididymitis on the right side, was operated upon by Dr. George Mueller with a diathermy knife and began to

improve in health and weight. Some time later he developed involvement of the left epididymis, but this opened spontaneously and soon healed. He lost a year at medical school but later concluded his course and internship. In 1928, rectal examination revealed some involvement of prostate and seminal vesicles, the right one especially, and later an involvement of the right testicle which became moderately enlarged and a hydrocele developed. He then consulted Dr. Hugh Young in Baltimore who advised widespread removal of the affected organs, without which Dr. Young said the patient would not live ten years. Operation was not accepted but he continued to gain, adding about 30 pounds in a few years, appearing well and leading an active life, his weight exceeding any previous period. This state of well being continued until tubercle bacilli were found in his urine and even for some time thereafter. Then began a series of cystoscopies and intravenous pyelograms at the hands of Dr. Lorenzo Milliken who removed a tuberculous kidney in April, 1943. A loss of 10 pounds followed; this was only partly regained but he resumed his activities. Tubercle bacilli did not disappear from the urine however.

Early in 1944 he developed a deep urethral obstruction, believed by Dr. Milliken to have been due to a tuberculous lesion. Again he was hospitalized and the stricture dilated. This had to be followed for a time by instrumentation and at times by catheterization. Slight hematuria persisted. Quite possibly the instrumentation was the source of a colon infection and of a severe illness which again required hospital care. He was admitted on September 25, 1945. Chill, temperature rise to 104°F. and colon bacilli were found in blood stream and urine and numbers of *Mycobacterium tuberculosis* also in urine, singly and in clusters. The colon infection suggested the use of streptomycin and this was obtained on October 8, 1945, through Dr. J. M. Carlisle of Merck & Company who suggested that we begin with three million units every twenty-four hours. Meanwhile his urine was kept at a pH of 5 to 5.5 and he was given glucose and saline and whole blood transfusions. Fever subsided gradually, reaching normal in a week but on October 6, 1945, eleven days after admission, he had a chill, temperature rose from 98°F. to 103.4°F. and to 104.4°F. the next two days, typical spiked elevations. His urine became very thick and had the appearance and consistency of dirty cream, due to pus with

some blood. Blood cultures became negative for colon organisms in forty-eight hours but they persisted in the urine until streptomycin had been given for five days. Urine culture was positive for colon organisms on October 5th, streptomycin was begun on October 8th and the next urine culture on October 13th, was negative and remained negative. Acid-fast bacilli disappeared on October 17th, nine days after streptomycin was begun, remained absent on smears, culture and by guinea pig inoculation for a period of eight months when they reappeared. At this time we were able to procure 8 Gm. of the antibiotic and again the acid-fast bacilli began to disappear to the extent that they were difficult to find. He had received streptomycin originally from October 8th to November 19, 1945, this being continued after his return home on November, 2 1945, until a total of 35 million units (35 Gm. of the hydrochloride) had been given, 3 million units daily for three days, 2 million for one day, then $1\frac{1}{2}$ million for one day, followed by one million units October 27, 1945. Three days elapsed before a new supply was received. This was given in daily doses of $\frac{1}{2}$ million units, in part because of the difficulty in obtaining the drug and in part because of his reaction. He had been seriously ill but because of the severe headache, prostration, chilliness and vertigo which attended the large doses, it seemed expedient to reduce the daily amount. The urine cleared rapidly, pus disappeared, but traces of blood persisted, the volume increased and temperature became normal five days after the streptomycin was first given, at four-hour intervals subcutaneously. There was no consistent drop in blood pressure which could be ascribed to the drug. The CO_2 combining power was 49 mgs. per cent and blood urea nitrogen 16 mg. per cent on admission. This rose gradually to 42 vols. per cent on October 29, 1945 but fell gradually to normal and has since remained normal. Red cell counts and hemoglobin were good at all times, practically normal, but leukocytes remained high throughout, from 23,600 on admission to 39,800 on October 7, 1945, to fall slowly after the streptomycin was started on October 8th but not to normal. Many young forms were usually present and a definite left shift. Reticulocyte counts ranged from 0.3 per cent to 0.5 per cent. We have noted an elevation of blood urea in another patient receiving streptomycin but cannot say unequivocally that this is due to

the drug. If it were, the effect is not likely to be parenchymatous, judging from cases of uncomplicated nephrosis where blood urea levels are relatively normal. One would expect it to be due to vascular and perivascular irritation thus involving the glomeruli.⁹

Specimens collected October 25, 1945, when the patient was receiving one million units every twenty-four hours were as follows: Serum concentration 15.1 units per cc., approximately 7.5 units per cc. of whole blood, urine concentration 256 units per cc. Determinations also were made separately on these specimens by an experienced person. The figures reveal a striking similarity. Serum concentration 16 units per cc., representing 8 units per cc. of whole blood; urine concentration 60 units per cc. The organism used in all of the studies was the staphylococcus, S. M. strain furnished us through the courtesy of Merck & Company. A specimen of this urine, centrifuged at high speed, contained innumerable red blood cells and many leukocytes but was negative for organisms, including acid-fast bacilli.

A second series of specimens collected November 9, 1945, the dosage of streptomycin now being 500,000 units per twenty-four hours, revealed: Serum concentration of 10.6 units per cc., or approximately 5.5 units per cc. of whole blood; urine concentration 245 units per cc.; urine output about 2200 cc. in twenty four hours. Duplicate studies in another laboratory as previously noted, using the same S.M. strain staphylococcus, showed serum concentration of 14.6 units per cc.; urine concentration 271 units per cc. There were only a few red cells and an occasional white cell present in the urine, but no acid-fast bacilli.

A third study made when only 500,000 units were being given every forty-eight hours disclosed a serum concentration of 8.6 units per cc., or approximately 4.3 units per cc. of whole blood; urine concentration 96.4 units per cc.; negative for tubercle bacilli and relatively few red blood cells in the sediment of a 100 cc. centrifuged specimen.

The patient convalesced slowly, His heart rate varied from 100 to 120 on slight effort which was not explained upon physical examination. He gradually resumed his professional duties under limited conditions. Early in the following March of 1946 he had a temporary upset, slight sore throat, headache, malaise and a little temperature rise with pulse still rapid.

The patient elected to take penicillin orally, 250,000 units per day. The blood level was determined nearly twenty-four hours after the last dose, hence it was less than one unit per cc. of serum. The urine volume was 1950 cc. in twenty-four hours, 2 units per cc. or 3900 units in twenty-four hours. Blood was present microscopically but no acid-fast bacilli were found. Blood urea nitrogen was 12 mg. per cent. After four weeks of incubation culture was negative for acid-fast organisms. Early in April, 1946, blood count showed a slight microcytic anemia with 7100 leukocytes, normal differential. Blood urea nitrogen was again 12 mg. per cent and creatinin 1.5 mg. per cent. Early in July, 1946, tubercle bacilli were again found in the urine; also many pus cells and erythrocytes and, on culture of urine, staphylococcus albus, non-hemolytic streptococci and diphtheroids. Fortunately a small amount of streptomycin was obtained and he was given one million units daily for four days. After receiving 2,125,000 units by subcutaneous injection, the serum level was $9\frac{1}{2}$ units, the urine level 252 units per cc., an approximate recovery of 56 per cent in the urine. Many acid-fast bacilli were found. He reacted promptly to the drug, not having had any for eight months. He received one million units daily by subcutaneous injection for four days but his malaise became profound, he again developed headache and vertigo, although he did not complain of deafness and he developed a fever of a little over 100°F . Incapacitated for work, he begged for smaller doses. Streptomycin was reduced to 250,000 units every twenty-four hours, given at six-hour intervals, largely because the total supply of streptomycin was limited. This episode was rather more suggestive of a sensitizing reaction than of any toxic property in the drug itself. His blood pressure, usually 100 to 110 systolic, fell to 90 systolic and 60 diastolic during the attack. Another determination of the levels was made between the second and third days of a dosage of one million units per day intramuscularly: Serum level 9.5 units; urine level 252 units, a recovery of about 56 per cent. Acid-fast bacilli were present and not difficult to find.

Neither the time factor nor the dose had thus far made any definite impress. In the initial period of streptomycin dosage, eight months prior, the three days of three million units per day, followed by a gradual reduction may have

avoided any possibility of drug fastness. It is certain that the total disappearance of the organism, the gain in weight and return to physical efficiency in this patient gave evidence of at least bacteriostatic action of the drug and encourage the hope that an available supply and sufficient dosage of streptomycin may arrest an incipient case of tuberculosis and restore efficiency for gainful occupation in one even with such diverse and widespread manifestations as presented by this patient. Of course, the long period of infection may have resulted in some degree of immunization.

COMMENTS

Dr. Waksman¹⁰ has been working with the Actinomyces group of soil organisms since 1919, but it was not until 1940 that he produced streptothricin obtained from *Streptomyces lavendulae*,¹¹ the first antibiotic capable of acting against both gram-positive and gram-negative organisms. In 1944,¹² streptomycin was produced from *Streptomyces griseus*. This has proved to be relatively non-toxic in the doses thus far employed. A histamine-like¹³ reaction may occur, especially when, for any reason, the drug has been stopped, to be used again after a lapse of some weeks. The drug has been proved active against a wide range of pathogenic organisms, both gram-positive and gram-negative.¹⁴ This has been true both *in vitro* and in experimental animals and against certain infections in humans. No two lots of streptomycin assay alike. The unit strength varies. These units of antibiotic substances express their antibacterial properties as measured against some test organism, ascertaining the smallest quantity of the drug necessary to inhibit the growth of staphylococci, *E. coli*, *B. subtilis* and a hemolytic organism such as *B. megatherium*,¹⁵ in 1 cc. of broth, using the slide cell or cup plate method. One thousand such units would assay about 300 to 800 units to 1 mg. of base, more nearly the latter. However, in any given case, the variability in unit strength as determined by assay of any known dilution, furnishes

proof that streptomycin is not as yet a pure product.

Enough evidence has been produced to prove its therapeutic efficacy, both in test animals and in man, in a limited number of diseases. No serious reactions have been thus far disclosed. In colon bacillus infection, Hemophilus influenza and in meningitis due to this latter organism, in the Salmonella group and the Friedländer infections,¹⁶ it has achieved its greatest triumphs. Despite the striking results *in vitro* with the typhoid organism, clinically it has been disappointing. Both experimental and clinical results offer a justifiable degree of hope, even of expectation. Tularemia^{17,18} also has been successfully treated but undulant fever is rebellious. The surgeon may find it of value in selected cases of wound infection, but it is too early to speak of this with certainty.

Method of administration is a matter of general agreement. Romansky and Dittman¹⁹ suggested the use of beeswax and sesame oil, of proved value in penicillin, to prolong the effect of streptomycin. Not enough evidence is extant to be able to make an unqualified statement as to blood and urine levels. Only one observer has reported induration and prolonged tenderness after many injections of streptomycin had been given.²⁰

SUMMARY

This is a report of a prompt response of a blood stream and genitourinary infection by colon bacilli in a man with widespread tuberculosis of long standing, which was arrested during the exhibition of streptomycin and eight months thereafter, during which restoration to working efficiency, some gain in weight and improved health were attained. Had it been possible to obtain the drug in necessary amount when needed, it is conceivable that more definite results might have followed. After the lapse of eight months, the patient received one million units of streptomycin base daily for

four days and subsequently, only 250,000 units daily for twelve days more (seven million units in sixteen days) and a specimen of 100 cc. of urine, centrifuged for one hour, failed to reveal tubercle bacilli after prolonged search. The drug was then stopped by mutual agreement because of the patient's anorexia, malaise and depression, associated with a lower blood pressure than he had ever had prior to this second period of streptomycin administration.

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Marked Insulin Resistance in Diabetes Mellitus*

MAXWELL G. BERRY, M.D. and FERDINAND C. HELWIG, M.D.

Kansas City, Missouri

INSULIN resistance is one of the striking complications encountered in the management of diabetes mellitus. No arbitrary limit to the dosage of insulin beyond which insulin resistance can be said to exist has been established. Patients in whom total pancreatectomy has been carried out can be maintained on insulin in doses varying from 26 to 40 units daily.¹ Severe diabetics frequently require more than this amount of insulin each day and are not classified as resistant to insulin. However, when an individual requires ten or even one hundred times this amount of insulin in twenty-four hours, it can be stated that in some manner he is resistant to the usual effects of the hormone.

Various conditions have been found to increase the requirements of insulin.² The possible causes for insulin resistance listed by Joslin and his associates³ are acidosis, infections, destructive processes in the pancreas, disturbance of liver function, complicating disease of other endocrine glands, hemochromatosis and disturbance in the function of the skin and muscles. Levi and Friedman⁴ report a case of extreme resistance to insulin in lymphatic leukemia. Daily administration of large doses of insulin to non-diabetic patients causes elevation of the glucose tolerance curve.⁵ Typhoid vaccine produces resistance to insulin in depancreatized dogs.⁶ Lerman⁷ believes antibody development and concentration is responsible for the development of insulin resistance. Lowell⁸ reports a case in which insulin resistance and allergic phenomena were present simultaneously. Thrombosis of the hepatic artery with

resistance to insulin was reported by Pollack and Long.⁹ Several cases requiring very large doses of insulin have been recorded. Wiener¹⁰ reported an instance in which he gave 3,250 units of insulin in twenty-four hours. Other cases have received in twenty-four hours 2,795 units,¹¹ 2,100 units,¹² 1,630 units,¹³ 1,297 units,¹⁴ 1,310 units,¹⁵ 1,205 units,¹⁶ and 1,720 units,¹⁷ 4,000 units a day for four successive days,⁴ 2,460 units in twenty-four hours,¹⁸ 3,620 units in twenty hours¹⁹ and 5,780 units in twenty-four hours²⁰ have also been reported.

The case which we are reporting is unusual in that 5,820 units of insulin were administered in twenty-four hours (5,460 in twenty hours). We are unable to find record of a patient who received as large an amount of insulin in this period of time.

CASE REPORT

W. M. C., a sixty-six year old white banker, was admitted to St. Luke's Hospital on December 23, 1940. He had been known to have diabetes for two years and this had been controlled by diet without insulin until two months before admission when increased thirst and polyuria developed. Since December 9, 1940, he had received 25 units of regular insulin daily but the urine had persistently contained sugar. Since December 16th he had been nauseated and for three days prior to admission he had vomited everything taken by mouth.

On admission he was mentally alert, there was no air hunger, but he was obviously weak and tired. The temperature was 98.0°F., pulse 100, blood pressure 180 systolic and 90 diastolic; there was marked pyorrhea and the pharynx was moderately red. There was a slight accentuation of the second aortic heart sound, the rhythm

* From the Departments of Medicine and Pathology, St. Luke's Hospital, Kansas City, Mo.

was regular. The non-tender liver edge was palpable a finger's breadth below the costal margin. There was slight pitting edema of both ankles.

The urine contained a trace of albumin, 4 plus sugar, 1 plus acetone and the specific gravity

TABLE I

Date	Blood Sugar		Urine Sugar		CO ₂ Combining Power		Insulin Units
	High	Low	High	Low	High	Low	
12-23-40	570	357	+4	+4	36	..	210
12-24-40	317	190	+4	+2	48	..	390
12-25-40	238	130	...	0	270
12-26-40	259	204	+4	0	400
12-27-40	317	119	+4	0	40	..	610
12-28-40	317	120	+4	+1	36	..	750
12-29-40	219	109	+4	0	36	..	920
12-30-40	317	209	+4	+1	32	..	880
12-31-40	357	285	+4	+3	1,740
1-1-41	715	357	+4	+4	28	4	5,820
1-2-41	218	58	+1	0	52	..	200
1-3-41	197	105	+1	0	40
1-4-41	285	179	+3	0	48	..	460
1-5-41	571	285	+4	0	40	..	1,040
1-6-41	571	357	+4	+4	34	..	1,870
1-7-41	396	190	+4	0	42	..	1,250
1-8-41	179	89	+1	0	50	..	0
1-9-41	238	109	+1	0	40
1-10-41	317	238	+3	+2	42	..	240
1-11-41	420	315	+4	+3	40	..	1,610
1-12-41	317	57	+4	0	42	..	1,300
1-13-41	139	42	0	0	40	..	0
1-14-41	163	114	0	0	56	..	0
1-15-41	238	142	+3	0	56	..	110
1-16-41	..	142	...	0	0

was 1.033; the hemoglobin was 95 per cent, the red cell count 4,000,000 and the white cell count 6,600 with a normal differential count. The non-protein nitrogen was 50 mg. per 100 cc., creatinine 1.5 mg., the chlorides 400 mg., the cholesterol 150 mg. and the sugar 400 mg. Wassermann and Kline reactions were negative, the CO₂ combining power was 36 volumes per cent and the sedimentation rate was 20 mm. in one hour.

During the first day of hospitalization the blood sugar level remained high and the urine continued to contain sugar and acetone in spite of a total of 210 units of insulin. Marked insulin resistance continued and in spite of large doses, coma developed on January 1, 1941. Table I shows the high and low blood sugar, urine sugar and CO₂ combining power, together with insulin given during each twenty-four-hour period. Low grade fever was present from the first day, varying between 99.6 and 101°F. with the white blood cell count ranging between

5,600 and 10,300 and polymorphonuclear cells between 56 and 89 per cent.

Slight edema of the extremities persisted in spite of an adequate urinary output during the first eight days, and then increased as the output of urine diminished until there was a 3 to 4 plus edema of the entire lower extremities. Following marked acidosis on January 1st, the liver increased only slightly in size but ascites developed. Attempts at diuresis by various drugs failed although the specific gravity of the urine remained normal and there was never more than a heavy trace of albumin.

On the morning of January 1, 1941, the patient developed marked acidosis and coma. Insulin was given in increasing doses at intervals of about one-half hour. When it became apparent that the acidosis was increasing, insulin made by three different manufacturers in various strengths was given; three doses of protamine zinc insulin were also administered and the sites of injection were changed. In addition, 2,400 units of the total were administered intravenously. Finally one dose of 500 units of U100 insulin was given subcutaneously and following this injection the acidosis and coma responded more favorably. A total of 5,820 units was given in twenty-four hours. Almost 10,000 cc. of fluid, including 300 cc. of 5 per cent sodium bicarbonate, was given during the same period. During the morning of January 1st, after onset of the marked acidosis an attack of paroxysmal auricular tachycardia with a heart rate of 180 per minute occurred and lasted for twelve hours. Following this, the rhythm remained normal.

During the afternoon of January 2, 1941, he was mentally alert and dictated several business letters. However, the course was progressively downward from this day on. Terminally, he developed pulmonary edema and bronchopneumonia. The blood sugar one hour before death on January 16, 1941, was 142 mg. per 100 cc.

At necropsy the body showed generalized edema and the skin was faintly jaundiced. The peritoneal cavity contained about 600 cc. of clear straw-colored fluid. The peritoneal surfaces were slick and shiny except in the lesser sac in which foci of fat necrosis were observed.

The liver weighed 1,500 Gm., was moderately bile-stained and showed a low grade Laennec's cirrhosis. The gallbladder was not grossly inflamed, contained thick green mucoid bile and

three small irregular calculi, the largest measuring only 7 mm. in diameter. The pancreas did not appear particularly enlarged but the surface and repeated cross sections showed widely disseminated zones of fat necrosis throughout. The portal vein was dilated and measured about 4 cm. in circumference. The lumen was filled with a firm reddish thrombus which extended into the splenic vein; the intimal lining of both veins was smooth and shiny except near the spleen where the thrombus became firmly adherent to the endothelium. The spleen weighed 200 Gm. Its capsule was slightly wrinkled and about 2.5 cm. from the lower pole a raised area of infarction 1.5 cm. in diameter was seen. On cross section several smaller infarcts were observed. Between the infarcts the pulp was soft and showed a bluish-red mottled cut surface. The venous radicles within the spleen were dilated and filled with adherent red thrombi. The right femoral vein was occluded by a red thrombus in the upper thigh area. The other viscera showed little of gross interest aside from pulmonary edema with early bronchopneumonia, moderate benign prostatic hypertrophy and a moderate degree of cerebral edema.

On microscopic examination the liver showed a moderate increase in the perilobular fibrous tissue and considerable cloudy swelling of the parenchyma. Some foci of interstitial hemorrhage were seen and minature bile thrombi in many of the canaliculi were observed. There was also evidence of degeneration and regeneration of liver cells. The pancreas, in addition to rather marked fat necrosis, showed both interstitial hemorrhage and polynuclear leukocytic infiltration. The islets presented little notable alteration. The spleen showed thrombosis of the major venous channels and early infarction. The kidneys showed many fine focal scars infiltrated with lymphocytes. There was also advanced tubular degeneration and some bile staining of the tubular albumin. The portal and splenic veins showed laminated thrombi with classical lines of Zahn. Carmine stains of the various organs showed the liver to be poor in glycogen with little or none present elsewhere.

The anatomic diagnosis was acute disseminated pancreatitis with hemorrhage and fat necrosis; phlebothrombosis of the portal, splenic and right femoral veins; multiple infarcts of the spleen; early portal cirrhosis of the liver with cloudy swelling and bile thrombosis; cholelithiasis; bile nephrosis; pulmonary edema with

terminal bronchopneumonia; cerebral edema and generalized anasarca.

DISCUSSION

Delay in absorption and impotency of the insulin used were apparently not factors in the failure of this patient to respond to the usual doses of insulin. Lipocaiac was administered during the last ten days of his life without benefit.

CONCLUSION

The case of a man, sixty-six years old, who was treated for diabetic coma by administration of 5,820 units of insulin in twenty-four hours is reported with necropsy findings.

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Phosphorus Poisoning with Recovery Accompanied by Electrocardiographic Changes

ROBERT A. NEWBURGER M.D.,* SAMUEL B. BEASER M.D.†

New York, New York

Boston, Massachusetts

and HARRY SHWACHMAN M.D.‡

Boston, Massachusetts

WHITE phosphorus is well known as a protoplasmic poison, producing fatty degeneration and necrosis of cells. In phosphorus poisoning,¹ practically all the organs are involved, with the liver, heart and kidneys showing the greatest damage. The present report is that of a patient with phosphorus poisoning showing evidence of dysfunction of the heart, liver and hemopoietic system of moderate intensity and almost complete reversibility.

CASE REPORT

The patient was a twenty-one year old Puerto Rican soldier who was admitted to the hospital on May 20, 1945, shortly after midnight. Two or three hours earlier he had ingested, with suicidal intent, about 60 Gm. of a rat paste (Paste Electrica) containing $2\frac{1}{2}$ per cent white phosphorus according to the label. He had stirred the material into a glass of beer and drained the glass. As much as 1.5 Gm. of white phosphorus may have been so ingested.‡ Before admission the patient had vomited twice and complained of abdominal cramps. He was moderately uncomfortable when first examined. A gastric lavage was immediately performed, first with 60 cc. of 3 per cent hydrogen peroxide and then with 300 to 500 cc. of 1 per cent copper sulfate. After the lavage 90 cc. of 50 per cent magnesium sulfate was left in the stomach as a cathartic.²

§ Minimum lethal dose for adults is approximately 0.1 Gm.¹

* Assistant in Medicine, New York University College of Medicine; on leave of absence in the U. S. Army.

† Assistant in Medicine, Harvard Medical School; on leave of absence in the U. S. Army.

‡ Assistant in Pediatrics, Harvard Medical School; on leave of absence in the U. S. Army.

Physical examination revealed that the general condition of the patient on admission was good. His temperature was 97°F., pulse 88 and blood pressure 120/70. His breath had a garlic-like odor. The skin presented a grayish pallor and this persisted for two or three days. The heart sounds were of good quality and intensity; the lungs were clear and the abdominal examination was noteworthy only because of slight tenderness in the epigastric region. The liver and spleen were not palpable. The reflexes were physiologic.

Although the patient was rather restless and uncommunicative during the first eighteen hours, he became subdued and responsive thereafter. He vomited once during the night and had three watery stools. The next morning the garlic-like odor of his breath was still present. He complained of some upper abdominal soreness of diminishing intensity for about one week. Nausea was present for the first few days and anorexia for a few more. At the end of the first week the patient felt well. Treatment consisted of intravenous fluids daily for the first two days (2,000 cc. of 5 per cent glucose in normal saline with 10 mg. of thiamin chloride), and daily intramuscular injections of crude liver extract (2 cc.) and of 3.2 mg. of vitamin K for the first five days. The diet was high in carbohydrate and protein and low in fat. In addition he received psychiatric attention and was subjected to a variety of laboratory tests.

Laboratory findings consisted of the following: Blood: the red blood count and hemoglobin (photoelectric colorimeter) were normal through-

out. The white blood count (Table I) showed a transient leukopenia and neutropenia. Platelets appeared normal in number and morphology in all blood smears. All urines and repeated stools were normal. The gastric washings had a garlic-like odor but did not glow in the dark.

tests are shown in Table II. Other examinations were made with essentially normal findings as follows: Serum albumin, 3.7 Gm.; serum globulin, 3.0 Gm. on May 21st; prothrombin time, 17.0 seconds; control, 16.1 seconds on May 23rd; oral glucose tolerance test, (1.75 Gm.

TABLE I

Date	White Blood Cells Per Cu. mm.	Polymorphonuclear Leukocytes			Lymphocytes, Per cent	Eosinophiles, Per cent	Basophiles, Per cent	Mononuclears, Per cent
		Segmented, Per cent	Unsegmented, Per cent	Total, Per cent				
May 20	2,450	47	50	2	1	0
May 21	6,550	8	3	11	79	3	2	5
May 23	6,000	25	18	43	43	8	1	5
May 30	6,250	44	37	15	0	4
July 25	5,750	40	13	53	32	13	1	1

Tests showed the gastric contents to be strongly positive for inorganic phosphate (none were performed for free phosphorus). The sternal bone marrow obtained by needle puncture on

per Kg. body weight); fasting blood sugar, 93 mg. thirty minutes, 156 mg. one hour, 142 mg. two hours, 83 mg. three hours, 88 mg. on July 26th; icterus index of 6 and 7 on May 21st and 24th, respectively; galactose tolerance test, 0.57 Gm. of reducing substance excreted in the urine in five hours after ingestion of 40 Gm. of galactose on May 27th; blood cholesterol, 184 mg. on May 28th and bromsulphthalein test, 5 mg. per Kg. body weight, 0 per cent retention after thirty minutes on June 16th and again on September 15th.

An electrocardiogram was taken on May 22nd (two days after admission) and at less than weekly intervals thereafter. The first tracing showed lowered voltage of T₁, T₂ and T₄ and isoelectric T₃. The ascending limbs of T₁ and T₂ were straightened and T₄ assumed a concave-plane shape. It took fully one month for these changes to revert to normal, as seen in the accompanying illustration.

Roentgenograms of the forearm and wrist on July 28th were normal.

COMMENTS

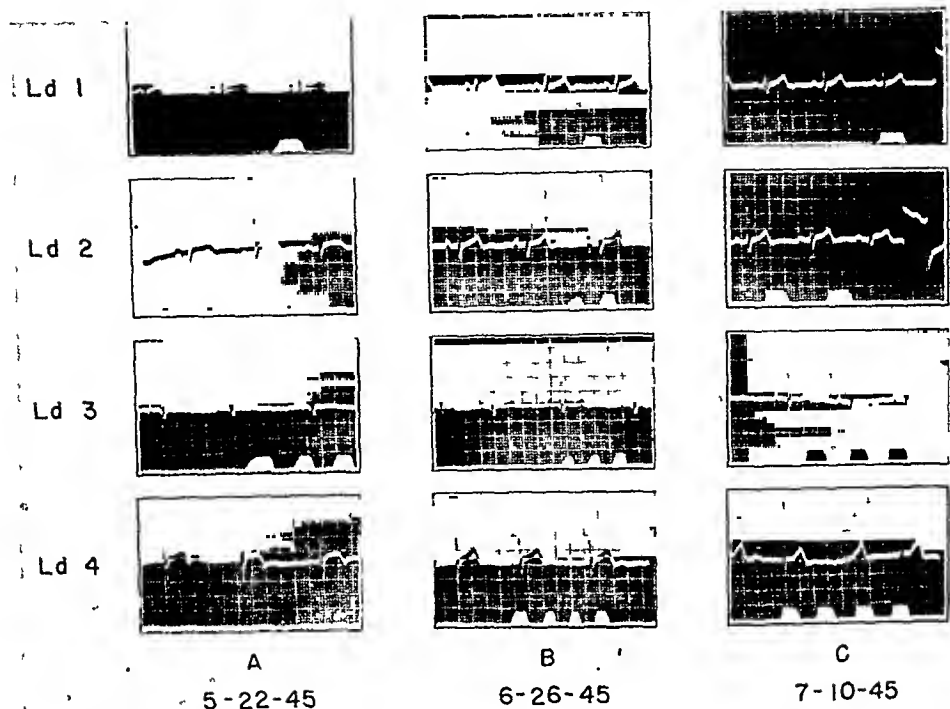
Various observations made on this patient are worthy of note. Leukopenia and neutropenia, although not alarming, were quite definite. Similar blood findings were present in the case reported by Chretien.³ Because of the transient nature of the change, it is conceivable that it may have been over-

TABLE II

Date	Non-protein Nitrogen mg. %	Urea Nitrogen mg. %	Cephalin-Cholesterol Flocculation Test (48 hours)	Intravenous Hippuric Acid Test: Gm. Benzoic Acid in Urine in One Hour (1.77 Gm. Sodium Benzoate)	Extren-Rose Glucose Tolerance Test		
					Fasting	½ hour	1 hour
May 21	54	13					
May 22..	4+				
May 24..	20	15					
May 25..	89	103	133
June 1...	4+	0.74	100	123	149
June 16..	3+	0.67			
July 3...	4+	..			
July 20..	102	106	138
July 25..	32	12	3+	0.58			
Aug. 20..	4+	..			
Sept. 3..	0.43	83	123	99
Sept. 20..	0.73			
Sept. 24..	1+				

May 23rd showed some toxic granulation of the granulocytes. There was no reduction in granulocyte activity and there appeared to be no maturation arrest.

Results of the various repeated liver function tests, blood non-protein nitrogen, blood urea nitrogen, and Extren-Rose glucose tolerance



Electrocardiograms A, B and C, taken two, thirty-seven and fifty-one days, respectively, after the ingestion of white phosphorus. Note in A the lowering of the voltage of T_1 , T_2 and T_4 and isoelectric T_3 , also the straightening of the ascending limb of T_1 and T_2 and the cone-plane shape of T_4 . Reversion toward normal is noted in the second tracing.

looked in other reported cases. The bone marrow, although obtained promptly, showed only minimal changes.*

The electrocardiographic changes, confined to moderate T wave abnormalities, are definite although not sufficiently characteristic to be considered specific. The causes of diminution in T wave voltage are many, but we are aware of only one other known case report of T wave changes attributable to phosphorus poisoning.⁴ The changes in that case were very similar to those of ours. An abrupt type of exitus, possibly cardiac in origin, has been described as occurring in the first day or two in cases of phosphorus poisonings.[†] The cardiovascular factor, which has usually been neglected both clinically and electrocardiographically in the reported cases of phosphorus poisoning, should be considered

more carefully in the future for information which may prove of value in treatment.

The evidence for significant acute liver involvement included an increased blood non-protein nitrogen level, concomitantly with a low normal blood urea nitrogen level. This abnormal ratio returned to normal in a relatively short time. Bile pigment metabolism remained intact throughout. The cephalin-cholesterol flocculation test of Hanger was abnormal when first done on May 22nd, and remained abnormal during a four-month period. The intravenous hippuric acid test for Quick became progressively abnormal until the final test on September 20th which gave a result within normal limits. This course of the liver damage stands in contrast to the rapidly reversible disturbance of the myocardium and the hemopoietic system, and is in accord with the well known hypersusceptibility of the liver to phosphorus.

SUMMARY

1. A case of ostensibly mild phosphorus poisoning is presented.

* Dr. William Dameshek was kind enough to review the bone marrow smears.

† Electrocardiographic changes of similar nature, and likewise unsuspected clinically, are described as occurring during the course of Fuadin therapy;⁵ after that, two, sudden deaths have been reported.

2. Changes were found in the hemopoietic, hepatic and cardiovascular systems.

3. The significance of the T wave changes in the electrocardiogram is discussed.

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